UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act

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1,4-Dioxane. Docket ID No.: EPA-HQ-OPPT-2016-0723.

1-Bromopropane. Docket ID No.: EPA-HQ-OPPT-2016-0741.

Asbestos. Docket ID No.: EPA-HQ-OPPT-2016-0736.

Carbon Tetrachloride. Docket ID No.: EPA-HQ-OPPT-2016-0733.

Cyclic Aliphatic Bromide Cluster (Hexabromocyclododecane or HBCD). Docket ID No.: EPA-HQ-OPPT-2016-0735.

Methylene Chloride. Docket ID No.: EPA-HQ-OPPT-2016-0742.

N-Methylpyrrolidone (NMP). Docket ID No.: EPA-HQ-OPPT-2016-0743.

Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f]diisoquinoline-1,3,8,10(2H,9H)-tetrone). Docket ID No.: EPA-HQ-OPPT-2016-0725.

Trichloroethylene (TCE). Docket ID No.: EPA-HQ-OPPT-2016-0737.

Tetrachloroethylene (also known as Perchloroethylene). Docket ID No.: EPA-HQ-OPPT-2016-0732.

INTRODUCTION AND SUMMARY

Safer Chemicals, Health Families (SCHF), Earthjustice, Natural Resources Defense Council (NRDC), Environmental Health Strategy Center, Toxic-Free Future and Asbestos Disease Awareness Organization (ADAO) submit these comments on the scoping documents developed by the Environmental Protection Agency (EPA) on the initial 10 chemicals selected for risk evaluations under the newly enacted Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA). These organizations are committed to enhancing the safety of chemicals used in homes, workplaces and products and strongly support effective and health-protective implementation of the LCSA.

Through LCSA, Congress amended the Toxic Substances Control Act (TSCA) to establish a new framework for conducting timely, comprehensive and science-based risk evaluations for chemicals of concern. The law provides that EPA's evaluations must be strictly risk-based and must result in a definitive determination of whether the evaluated substance as a whole presents an unreasonable risk of injury to health and the environment across its life cycle, without regard to cost and other non-risk factors.

Congress wanted EPA to launch the risk evaluation process expeditiously. Accordingly, in section 6(b)(2)(A) of TSCA, it directed EPA to assure that evaluations are initiated within six months of the law's enactment on 10 substances drawn from the 2014 TSCA Workplan list. EPA designated these 10 substances on December 19, 2016,[1] and following a public meeting and comment period, released draft scoping documents on June 22. Soon thereafter, EPA announced that it was developing problem formulation documents on the 10 chemicals and would release them for further comment by the end of the year. It also requested comments on the scoping documents in order to inform its approach to problem formulation.[2]

These comments address general issues common to the 10 chemicals as well as several chemical-specific issues. We are submitting our comments to all ten of the EPA dockets. The comments build on earlier submissions by these groups, including our March 15 comments on the scoping process and our July 24 letter to the Agency providing initial reactions to the 10 scoping documents. We have coordinated with a number of other public health and scientific organizations in developing comments on the scoping documents and generally support their recommendations.

The main messages and key recommendations in our comments are as follows:

- Problem formulation can fill gaps in scoping documents and enhance their depth of analysis but cannot be used to remove uses, exposures and hazards from the risk evaluation scope
- EPA should use problem formulation to provide more detail on the potentially exposed and susceptible subpopulations it will consider and how risks to these subpopulations will be determined
- Problem formulations should also describe EPA's strategies for assessing risks from aggregate and cumulative exposures
- Ongoing use and disposal of chemical products that are no longer being manufactured fall within the TSCA definition of "conditions of use" and must be included in problem formulations and assessed in risk evaluations
- Chemicals with ozone depletion and global warming potential pose environmental and health risks that fall within the scope of TSCA risk evaluations
- EPA risk evaluations should not reassess uses of trichloroethylene (TCE), methylene chloride (MC) and N-Methylpyrrolidone (NMP) that were fully assessed in its proposed section 6(a) rules, although these exposure pathways should be included in its determinations of aggregate exposure to these chemicals
- In the course of TSCA risk evaluations, EPA should not revisit definitive findings in IRIS assessments since these assessments represent the Agency's authoritative, peer reviewed determinations on the health effects of the chemicals they address
- In evaluating workplace risks, EPA should recognize and account for the uneven use and effectiveness of engineering controls, labeling and personal protective equipment in preventing occupational exposure and determine risks to workers in situations where these measures are not in place or ineffective
- EPA should not exclude from the 1,4-dioxane evaluation its production as a byproduct or impurity, which is a significant source of contamination of water sources and cancer risk

[1] 81 Federal Register 91927
[2] 82 Fed. Reg. 31,592 (July 7, 2017).

- In order to apply these general principles and fill other gaps in its scoping documents, these documents must be expanded and strengthened in several specific respects during problem formulation
- EPA should not prejudge the absence of adverse effects for particular end-points at the scoping stage but should defer such conclusions until the systematic review phase of its risk evaluation as the law requires
- Problem formulations should highlight aspects of use and exposure where available information is insufficient and request or require submission of this information by industry and other interested parties
- EPA needs to take stronger steps to limit CBI treatment of critical information during the risk evaluation process so that transparency and public participation in that process are not impaired

I. PROBLEM FORMULATION CAN FILL GAPS IN SCOPING DOCUMENTS AND ENHANCE THEIR DEPTH OF ANALYSIS BUT CANNOT BE USED TO REMOVE USES, EXPOSURES AND HAZARDS FROM THE RISK EVALUATION SCOPE

The 10 chemicals undergoing risk evaluations have widespread and substantial exposure and multiple adverse health effects. Comprehensive and health protective assessments of their safety are essential to safeguard communities and vulnerable populations and to set a precedent for strong and effective implementation of the new law. For this reason, our groups made a significant investment in characterizing the use and exposure profiles of several of the 10 chemicals and provided extensive submissions to the Agency to help inform its scoping documents for these chemicals.

The scoping documents represent a considerable amount of work in a short period of time and provide a helpful starting point for the 10 evaluations. However, the July 7 Federal Register notice announcing the availability of the scoping documents acknowledges that the Agency was unable to process all the information gathered during the scoping process and that the scoping documents were not as "refined or specific" as EPA had hoped. We agree with this assessment and believe that the scoping documents contain serious gaps, lack sufficient information on use and exposure, impose questionable limitations on the risk scenarios to be examined and fail to provide a roadmap to key elements of assessment methodology. These shortcomings reduce the utility of the scoping documents in laying the groundwork for well-informed and rigorous risk evaluations.

Given their limitations, we believe that expanding and strengthening the scoping documents through a problem formulation process is appropriate in this instance. However, neither LCSA nor the recently promulgated risk evaluation process rule refers to or authorizes problem formulation. Because it has no basis in the law, we oppose using problem formulation to narrow the scope of risk evaluations by deleting conditions of use, exposure pathways or health or environmental end-points identified in the June scoping documents. Section 6(b)(4)(D) of amended TSCA provides that, "not later than 6 months after the initiation of a risk evaluation," EPA must "publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and the potentially exposed or susceptible subpopulations the Administrator expects to consider." EPA met this requirement in its June scoping documents. The law provides no basis for EPA to remove uses, hazards or exposures from a risk

evaluation after its scope has been established in accordance with section 6(b)(4)(D).[3] Since problem formulation is not a recognized step in the risk evaluation process or a substitute for scoping under LCSA, it cannot be used narrow a risk evaluation's scope after-the-fact.

We do support, however, using problem formulation to provide more detail on the conditions of use, potentially exposed and susceptible subpopulations, and exposure pathways that EPA will evaluate as well as further explanation of the methodologies that EPA will use in its analysis of these and other risk assessment elements. This will help better structure the risk evaluations, assure that all relevant information is considered, and characterize more fully the conditions of use to be evaluated – without narrowing the risk evaluation scope.

II. EPA SHOULD USE PROBLEM FORMULATION TO PROVIDE MORE DETAIL ON THE POTENTIALLY EXPOSED AND SUSCEPTIBLE SUBPOPULATIONS IT WILL CONSIDER AND HOW RISKS TO THESE SUBPOPULATIONS WILL BE DETERMINED

One area that would benefit from greater elaboration during problem formulation is the identification of potentially exposed or susceptible subpopulations that require consideration in risk evaluations under TSCA section 6(b)(4)(F). The scoping documents provide nearly identical general "boilerplate" descriptions of such subpopulations. Further particulars on the size, geographic location, demographic characteristics and exposure profile of each subpopulation EPA has identified would provide helpful assurance that the risks to that subpopulation will be characterized with the rigor that TSCA requires.

It is also critical for EPA to spell out the methodology it intends to use to determine the nature and magnitude of the risks that chemicals pose to each subpopulation. Such subpopulations are often comprised of low income and/or people of color and exposed to a disproportionate share of pollution, environmental hazards, and social and economic stressors. Multiple exposures to chemical and non-chemical stressors collectively increase the risk of harm, combined with synergistic effects with other health stressors such as limited access to quality health care.[4,5] EPA's risk evaluations need to fully account for these factors and its problem formulations should explain how it intends to do so.

In regard to greater susceptibility, the following are well-known factors that increase biologic sensitivity or reduce resilience to exposures,[6,7] and should be considered consistently for all 10 chemicals to identify susceptible subpopulations:

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[3] EPA's final risk evaluation rule, in contrast to its proposal, would permit the Agency to select which conditions of use to include in risk evaluation scopes as opposed to including all such uses. 82 Fed. Reg. 33,726 (July 20, 2017). Our groups argued in their comments on the proposal that the law required the Agency to address all conditions of use in its risk evaluations, as was recognized in the Agency's original proposal. Along with several other groups, we are challenging EPA's contrary interpretation in its petition for judicial review of the risk evaluation rule. Regardless of the outcome of this challenge, we believe that EPA has no basis to narrow the risk evaluation to exclude conditions of use once they have been included in its scope.

[4] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

[5] Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. Meliker J, editor. PLoS One. 2017 Jul 12;12(7):e0176331.

[6] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

Intrinsic/ endogenous factors

- Genetic polymorphisms/ genetics/ genetic makeup
- Health status/ nutritional status/ disease status/ pre-existing conditions
- Prenatal life stage
- Age

Extrinsic factors

- Multiple exposures/ co-exposures
- Race/ ethnicity
- Socioeconomic status (SES)

For example, the prenatal life stage is the most sensitive to developmental and reproductive toxicants, and women of childbearing age should be considered as a susceptible subpopulation for any chemical with such hazards. However, women of reproductive age are not identified as a potential susceptible subpopulation in the scoping documents for pigment violet 29, TCE, NMP, PERC, or HBCD, even though EPA will consider reproductive and developmental toxicity hazards for these chemicals. This omission should be corrected during problem formulation.

III. PROBLEM FORMULATION MUST DESCRIBE EPA'S STRATEGIES FOR ASSESSING RISKS FROM AGGREGATE AND CUMULATIVE EXPOSURES

Problem formulation should also address more fully how EPA intends to address the risks resulting from cumulative and aggregate exposures to each of the 10 chemicals. The scoping documents provide minimal discussion of this essential aspect of risk evaluation design.

Section 6(b)(4)(F)(ii) requires risk evaluations to describe whether aggregate or sentinel exposures to a chemical were considered and the basis for that consideration. To properly apply either or both of these approaches in a risk evaluation, EPA must determine in advance what methodology it will employ and then incorporate it in the risk evaluation design in sufficient detail to describe the key data sources it will use to assess exposure and how they will be used. The scoping documents fail to do this. EPA should remedy this gap in problem formulation.

We believe aggregate exposure assessment will be required for all of the 10 chemicals.[8] The focus of the new law is on determining risk based on all relevant pathways and sources of exposure for the general population and vulnerable subpopulations throughout a chemical's life cycle. Thus, under section 6(b)(4)(F)(i), EPA must "integrate and assess available information on hazards and exposures for *the conditions of use* of the chemical substance" and, under section 6(b)(4)(F)(iv), must "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under *the conditions of use* of the chemical substance." This emphasis on integrating risk and exposure factors across a chemical's conditions of use necessarily requires the Agency to identify all sources of exposure that may affect the general population or specific subpopulations and to determine the overall levels, frequency

[7] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

[8] When analyzing aggregate exposures, "sentinel exposure" may be considered simultaneously, where appropriate. However, these are not mutually exclusive and EPA should not incorporate sentinel to the exclusion of aggregate.

and duration of exposures by each population or subpopulation resulting from this combination of pathways.[9]

EPA has applied the tools of "aggregate exposure assessment" successfully in several programs. For example, the 1996 Food Quality Protection Act (FQPA) directs EPA to examine aggregate exposures when issuing or renewing tolerances for pesticides in food and EPA has longstanding guidance for doing aggregate risk and exposure assessments to meet this requirement.[10]

During problem formulation, EPA should develop a roadmap for each of the 10 chemicals showing what steps it is taking to gather the necessary information for aggregate exposure assessment and how it will calculate or estimate the combined exposures resulting from multiple pathways or uses for the general population and potentially exposed or susceptible subpopulations.

Problem formulations should also address whether and how EPA will use "cumulative risk" methodologies for the first 10 risk evaluations. This, too, is an area that EPA has addressed in several guidance documents.[11] The Agency defines "cumulative risk" as "the combined risks from aggregate exposures (i.e., multiple route exposures) to multiple agents or stressors" and has explained that:

> "In cumulative risk assessments that examine risks posed by multiple chemicals, exposure assessments evaluate a population's chemical exposures through multiple routes of exposure over time. Such assessments may encompass multiple exposure timeframes in which the timing and intensity of exposures to different chemicals are examined relative to each other. It is also important to determine whether the exposures to multiple chemicals can lead to toxicokinetic interactions or toxicodynamic interactions. In addition to providing information about multiple chemical exposures in the general population, these exposure assessments identify potentially susceptible or vulnerable subpopulations in the study area and potentially unique pathways of exposure in those subpopulations."[12]

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[9] Exposures from TSCA-exempt uses such as personal care products or biocides should also be included in scoping documents and risk evaluations because of the need to account for their contribution to aggregate risk, even though regulatory authority over these products is not available under TSCA but derives from other laws administered by EPA or agencies such as FDA. This is now standard practice in implementing the Food Quality Protection Act (FQPA). The scoping documents contain limited and incomplete information on exposures to the listed chemicals from non-TSCA uses.

[10] https://www.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf

[11] E.g., *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity.* U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. (2002) Available at http://www.epa.gov/oppfead1/trac/science/cumulative_guidance.pdf; *Framework for Cumulative Risk Assessment,* U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/P-02/001F (2004). Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

[12] EPA National Center for Environmental Assessment, *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document,* at xxviii (August 2007).

The importance of examining risks posed by multiple chemicals with overlapping pathways of exposure and common adverse health effects was also underscored by the National Academy of Sciences (NAS) in its Phthalates and Cumulative Risk report.[13]

We recommend that, in its problem formulations, EPA should commit to perform cumulative risk assessments whenever a population or subpopulation exposed to the subject chemical is also exposed to other chemicals that have similar health effects. In this situation, total risk to the relevant population or subpopulation will be a function not just of exposure to the subject chemical in isolation but of combined exposure to that chemical and other chemicals which have additive or synergistic health effects.

A compelling case for examining cumulative risks will exist where EPA is in parallel conducting risk evaluations on multiple chemicals within a class that have similar chemical structures, conditions of use and adverse health effects. An example of such a grouping is the four solvents (TCE, PERC, MC and NMP) among the initial 10 chemicals: not only is it likely that workers and consumers are exposed to all or some of these solvents simultaneously but their common hazards (i.e. neurotoxicity, reproductive toxicity) are likely to magnify the risks of such concurrent exposures. The problem formulations for these four chemicals should recognize the need to examine the cumulative risks they present and describe how EPA will evaluate cumulative risk scenarios.

IV. ONGOING USE AND DISPOSAL OF CHEMICAL PRODUCTS THAT ARE NO LONGER BEING MANUFACTURED FALL WITHIN THE TSCA DEFINITION OF "CONDITIONS OF USE" AND MUST BE ASSESSED IN RISK EVALUATIONS

Several of the 10 chemicals – asbestos, perchloroethylene (PERC), TCE, MC, carbon tetrachloride (CTC) and hexabromocyclododecane (HBCD) – contribute to ongoing exposure and risk as a result of historical manufacturing and processing activities that have been discontinued. In many cases, the current and foreseeable risks associated with these activities are significant. Nonetheless, the scoping documents provide limited information about these risk and exposure scenarios and take the position that they are outside the scope of risk evaluations except possibly as a source of information about aggregate exposure. Each scoping document contains this statement:

> "EPA interprets the mandates under section 6(a)-(b) to conduct risk evaluations and any corresponding risk management to focus on uses for which manufacture, processing, or distribution in commerce is intended, known to be occurring, or reasonably foreseen (i.e., is prospective or on-going), rather than reaching back to evaluate the risks associated with legacy uses, associated disposal, and legacy disposal, and interprets the definition of "conditions of use" in that context. For instance, the conditions of use for purposes of section 6 might reasonably include the use of a chemical substance in insulation where the manufacture, processing or distribution in commerce for that use is prospective or on-going, but would not include the use of the chemical substance in previously installed insulation, if the manufacture, processing or distribution for that use is not prospective or on-going. In other words, EPA interprets the risk evaluation process of section 6 to focus on the continuing flow of chemical

[13] National Research Council. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies. 2008. Phthalates and cumulative risk assessment: the task ahead. Washington, D.C.: National Academies Press.

substances from manufacture, processing and distribution in commerce into the use and disposal stages of their lifecycle. That said, in a particular risk evaluation, EPA may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses."[14]

We believe that EPA is incorrectly interpreting the provisions of LCSA. The definition of "conditions of use" in section 3(4) covers the "circumstances . . . under which a chemical substance is . . . known or reasonably foreseen to be . . . used or disposed of." Where a chemical is performing an ongoing *in situ* function as a result of previous manufacturing and processing activity, that function comprises a current "use" of the chemical that is "known" to be occurring.

For example, although asbestos may no longer be sold as insulation, the asbestos insulation installed in millions of US buildings continues to perform insulating functions and thus is a current ongoing "use" of asbestos. Installed asbestos-containing building materials (ACBMs) represent one of the largest sources of asbestos accessible to the general public in the US, and the largest asbestos-exposed population consists of people who occupy buildings and homes with ACBMs. Maintenance and construction activities involving ACBMs are also frequent and widespread and account for the largest present-day increase in mesothelioma illness and death in the US.[15]

Similarly, the Healthy Building Network estimates there are 66-132 million pounds (30,000-60,000 metric tons) of HBCD in insulation in existing buildings.[16] These ongoing insulation uses are and will continue to be critical sources of ongoing exposures. HBCD is also present in cars and furniture as a flame retardant and its use in these long-lived consumer articles will contribute to ongoing exposures for years to come.[17]

Equally important, the disposal of building materials or consumer products containing asbestos or HBCD is an ongoing occurrence as buildings are torn down or remodeled and cars and furniture are replaced. Thus, the resulting releases into the environment and communities comprise a "circumstance . . . under which [these chemicals] are . . . known or reasonably foreseen to be . . . disposed of." As "conditions of use" within the TSCA definition, these activities and the risks they present are likewise required to be addressed in risk evaluations under section 6(b). For both chemicals, the immediate and long-term exposures associated with disposal of *in situ* building materials and products are likely to be widespread and significant well into the future.

To exclude from risk evaluations ongoing and future exposures from *in situ* uses of discontinued products would create a sizable gap in the life-cycle assessments of risk that Congress directed EPA to conduct under the new law. This would deprive the public, scientists and regulators of a comprehensive

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[14] EPA, *Scope of the Risk Evaluation for Asbestos*, June 2017, at 8.

[15] US CDC study, "Malignant Mesothelioma Mortality – United States 1999 to 2005."

[16] Safer Chemicals, Healthy Families et al. Comments to the U.S. Environmental Protection Agency (EPA) on the Scope of its Risk Evaluation for the TSCA Work Plan Chemicals: CYCLIC ALIPHATIC BROMIDE CLUSTER or HEXABROMOCYCLODODECANE (HBCD). March 15, 2017. https://healthybuilding.net/uploads/files/saferchemicals-hbcd.pdf

[17] For chemicals like TCE and PERC, the uses that contributed to widespread contamination of groundwater and drinking water may in fact be uses for which these chemicals are still being sold, requiring EPA to include them in its risk evaluations even under its narrow interpretation of the law.

picture of one of the largest sources of continuing and future risk. One consequence would be that EPA would lack the scientific basis to ban resumption of the sale and distribution of discontinued products containing asbestos, HBCD and similar chemicals despite the unreasonable risks that they present. In addition, decision-makers would be unable to reduce ongoing exposures and impose safeguards against unsafe disposal because they would lack a meaningful risk evaluation to inform these actions. Just as TSCA provides authority to evaluate the risks associated with ongoing exposures from discontinued activities, so it gives EPA the authority under section 6(a) to reduce these risks, yet the Agency would be stymied by the absence of a risk evaluation that provides a basis for such regulation.[18]

In short, EPA must characterize and assess ongoing exposures from the use and disposal of discontinued products and determine the risks they present as part of its risk evaluations on the initial 10 chemicals. The scoping documents provide virtually no discussion of these sources of exposure to the 10 chemicals. Nothing in the law allows EPA to exclude these risks from its evaluations. EPA must correct this omission during problem formulation.

V. OZONE DEPLETION AND GLOBAL WARMING POTENTIAL POSE ENVIRONMENTAL AND HEALTH RISKS THAT FALL WITHIN THE SCOPE OF TSCA RISK EVALUATIONS

In earlier submissions, SCHF and its members highlighted data showing the high ozone depleting potential of MC, CTC and 1-Bromopropane (1-BP).[19] The scoping documents do not address these properties of the three chemicals. Nor do they examine the global warming potential (GWP) of any of the 10 chemicals. These omissions conflict with the express purpose of risk evaluations under section 6(b)(4)(A): to "determine whether a chemical substance presents an unreasonable risk of injury to health *or the environment"* (emphasis added). They also fail to meet the Agency's obligation under section 6(b)(4)(F)(i) to "integrate and assess information . . . that is relevant to specific risks of injury to health *or the environment"* (emphasis added). Ozone depletion and global warming potential clearly pose risks to the environment and they are also recognized risk factors for human health.[20,21] Nothing in the law allows EPA to exclude these risks from its evaluations.

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[18] For some chemicals like lead and asbestos, other laws administered by EPA address handling and disposal of *in situ* materials. The Agency may be able to refer the findings of its risk evaluations to the programs implementing these laws under TSCA section 9(b) in lieu of further regulation under section 6. However, there are no existing laws that address ongoing exposure from use and disposal of discontinued products containing HBCD, perfluorinated chemicals and other substances and therefore the availability of the protections afforded under section 6 of TSCA may be critical to addressing their risks.

[19] See Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act, March 15, 2017.

[20] The human health risks of ozone depletion are well recognized by the Agency and documented, at least in part, on EPA's webpage, "Health and Environmental Effects of Ozone Layer Depletion:" "Ozone layer depletion increases the amount of UVB that reaches the Earth's surface. Laboratory and epidemiological studies demonstrate that UVB causes non-melanoma skin cancer and plays a major role in malignant melanoma development. In addition, UVB has been linked to the development of cataracts, a clouding of the eye's lens." https://www.epa.gov/ozone-layer-protection/health-and-environmental-effects-ozone-layer-depletion (Accessed 9-18-17)

[21] The human health risks of global warming were well recognized and documented, at least in part, by the agency prior to the arrival of Administrator Pruitt, as outlined in the legacy pages at: https://19january2017snapshot.epa.gov/climate-impacts/climate-impacts-human-health_.html While that page is being updated, "...to reflect EPA's priorities under the leadership of President Trump and Administrator Pruitt," the Agency still notes, "Climate change is having direct and indirect impacts on the health of people. More extreme

The EPA Office of Air and Radiation (OAR) has considerable expertise in both ozone depletion and global warming and has assessed some (but not all) of the 10 chemicals from the perspective of these concerns. OAR can help OCSPP draw on this prior work for its TSCA risk evaluations and perform new assessments for those chemicals whose ozone depletion and global warming impacts have not previously been examined. By addressing these impacts in TSCA risk evaluations, EPA will fulfill the law's goal of providing a comprehensive picture of environmental and health risks across the chemical's life cycle. In particular cases, it may also highlight contributors to ozone depletion and global warming that have been overlooked and may warrant restriction. Whether these impacts can be adequately addressed under the Clean Air Act (CAA) or under TSCA need not be determined in the risk evaluation itself and can be deferred to the later evaluation of risk management options under section 6(a).

VI. EPA RISK EVALUATIONS SHOULD NOT REASSESS USES OF TCE, MC AND NMP THAT WERE FULLY ASSESSED IN ITS PROPOSED SECTION 6(a) RULES

EPA has proposed to ban certain uses of TCE, MC and NMP under section 6(a) of amended TSCA.[22] As the basis for these proposed rules, EPA conducted comprehensive exposure and risk assessments on the targeted uses of the three chemicals. These assessments were subject to public comment and peer review both during their development and again as part of the rulemaking process.

In its scoping documents for the three chemicals, EPA indicates that it intends to rely on the completed assessments and will not "reassess" the targeted uses.[23] We strongly agree with this approach. It would be counterproductive for the Agency reopen these assessments for yet another round of public input and to redo the extensive analysis they contain simply so industry commenters can have another bite at the apple on findings they dislike. Moreover, we believe that the next step in the rulemakings is for EPA to issue final rules as quickly as possible. These rules, once issued, should close the book on the targeted uses and enable EPA to focus its risk evaluations on uses that have not yet been assessed. In its more comprehensive risk evaluations, however, EPA should incorporate its earlier assessments so that the exposures they describe can be accounted for in determining aggregate exposure to the three chemicals.

VII. EPA SHOULD NOT REVISIT DEFINITIVE FINDINGS IN IRIS ASSESSMENTS, WHICH REPRESENT THE AGENCY'S AUTHORITATIVE PEER-REVIEWED DETERMINATIONS OF THE HEALTH EFFECTS OF CHEMICALS

Five of the 10 chemicals – TCE, MC, CTC, PERC and 1,4-dioxane – have been assessed under the EPA Integrated Risk Information System (IRIS). The IRIS process is the Agency's authoritative mechanism for reviewing available studies, characterizing the health effects of chemicals and identifying concentrations below which these chemicals are not likely to cause adverse effects. IRIS assessments typically reflect

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weather events, heat waves, spread of infectious diseases and detrimental impacts on air and water quality are having impacts on our health." https://www.epa.gov/climate-research/human-health-and-climate-change-research (accessed 9-18-17).

[22] Trichloroethylene (TCE); Regulation of Use in Vapor Degreasing under TSCA Section 6(a), 82 Fed. Reg. 7432 (Jan. 19, 2017); Trichloroethylene; Regulation of Certain Uses under TSCA § 6(a), 81 Fed. Reg. 91592 (Dec. 16, 2016) and Methylene Chloride and N-Methylpyrrolidone; Regulation of Certain Uses under TSCA Section 6(a), 82 Fed. Reg. 7464 (Jan. 19, 2017).

[23] See, e.g., EPA. *Scope of the Risk Evaluation for Trichloroethylene,* June 2017, at 33.

years of work by EPA scientists, multiple rounds of public comment, inter and intra-agency consultation, and extensive peer review, often by the Agency's independent Science Advisory Board (SAB) or the National Academy of Sciences (NAS).

Where EPA is conducting a TSCA risk evaluation of a chemical that has already been assessed under IRIS, the conclusions of the IRIS assessment should be presumed to be applicable to the TSCA evaluation as a definitive statement by the Agency of the best available science. To revisit IRIS findings would be inefficient and resource-intensive at a time when the Agency is struggling with workforce and budget reductions. It would also make the three-year statutory deadline for completing risk evaluations even more challenging by greatly expanding the scope of EPA's work effort. Most significantly, reopening IRIS findings would prolong scientific uncertainty on issues that have been addressed and resolved through an authoritative, transparent and inclusive EPA process. Like other Agency actions, IRIS assessments often give rise to differences of opinion and some stakeholders may be disappointed by the outcome. But this does not mean that EPA should reinvent the wheel and provide another bite at the apple on scientific determinations that have been made after thorough deliberation and a robust process.

In sum, the problem formulation documents on the 10 chemicals should make clear that EPA's risk evaluations will rely on previous IRIS assessments in determining health effects that those assessments address.

VIII. IN EVALUATING WORKPLACE RISKS, EPA SHOULD RECOGNIZE THE UNEVEN USE AND EFFECTIVENESS OF ENGINEERING CONTROLS, LABELING AND PERSONAL PROTECTIVE EQUIPMENT IN PREVENTING OCCUPATIONAL EXPOSURE

Several scoping documents indicate that, in its approach to occupational exposure analysis, EPA will "[c]onsider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios."[24] These measures are certainly relevant factors in analyzing occupational exposures. However, it is essential that EPA not presume that they will be effective in preventing exposure in all workplaces and for all employees. In many cases, they may in fact provide limited protection, particularly for short-term poorly trained workers in small shops and workers whose English language skills are challenged.

In its proposed section 6(a) rules for TCE, MC and NMP, EPA explained at some length why label warnings and instructions are not uniformly read, comprehended or followed and thus provide limited protection. This was not a mere opinion on EPA's part but the result of an examination of nearly fifty studies.[25] Based on this review, EPA's conclusions as described in its initial TCE rulemaking were as follows:

> "The Agency determined that warning labels and instructions alone could not mitigate the risks to the extent necessary so that TCE no longer presents the identified unreasonable risks to users. The Agency based this determination on an analysis of 48 relevant studies or meta-analyses, which found that consumers and professionals do not consistently pay attention to

[24] See, for example, US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg. 45

[25] OPPT summarized these studies in a paper entitled *The Effectiveness of Labeling on Hazardous Chemicals and Other Products* (March 2016)(Ref. 33 in rulemaking docket).

labels; consumers and professional users often do not understand label information; consumers and professional users often base a decision to follow label information on previous experience and perceptions of risk; even if consumers and professional users have noticed, read, understood, and believed the information on a hazardous chemical product label, they may not be motivated to follow the label information, instructions, or warnings; and consumers and professional users have varying behavioral responses to warning labels, as shown by mixed results in studies."[26]

In the TCE vapor degreasing proposal, EPA further concluded that comprehension of warnings would be unusually challenging because of the complexity of the information conveyed:

> "EPA found that presenting information about TCE on a label would not adequately address the identified unreasonable risks because the nature of the information the user would need to read, understand, and act upon is extremely complex. It would be challenging to most users to follow or convey the complex product label instructions required to explain how to reduce exposures to the extremely low levels needed to minimize the risk from TCE. Rather than a simple message, the label would need to explain a variety of inter-related factors, including but not limited to the use of local exhaust ventilation, respirators and assigned protection factor for the user and bystanders, and time periods during pregnancy with susceptibility of the developing fetus to acute developmental effects, as well as effects to bystanders. *It is unlikely that label language changes for this use will result in widespread, consistent, and successful adoption of risk reduction measures by users and owners.*[27]

Similarly, EPA cautioned that "there are many documented limitations to successful implementation of respirators", including these well-known problems: [28]

> "Not all workers can wear respirators. Individuals with impaired lung function, due to asthma, emphysema, or chronic obstructive pulmonary disease for example, may be physically unable to wear a respirator. Determination of adequate fit and annual fit testing is required for a tight fitting full-face piece respirator to provide the required protection. Also, difficulties associated with selection, fit, and use often render them ineffective in actual application, preventing the assurance of consistent and reliable protection, regardless of the assigned capabilities of the respirator. Individuals who cannot get a good face piece fit, including those individuals whose beards or sideburns interfere with the face piece seal, would be unable to wear tight fitting respirators. In addition, respirators may also present communication problems, vision problems, worker fatigue and reduced work efficiency (63 FR 1156, January 8, 1998). According to OSHA, 'improperly selected respirators may afford no protection at all (for example, use of a dust mask against airborne vapors), may be so uncomfortable as to be intolerable to the wearer, or may hinder vision, communication, hearing, or movement and thus pose a risk to the wearer's safety or health. (63 FR 1189-1190).'"

EPA based these conclusions on expert analyses by OSHA, which has extensive experience with respirators under its workplace standards.

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[26] 81 FR at 91601.
[27] 82 FR 7441 (emphasis added)
[28] 82 FR 7445

The problem formulation documents should explicitly recognize that industrial hygiene controls do not necessarily provide reliable and effective protection from exposure and that the adequacy of these controls needs to be examined on a case-by-case basis in the context of the specific establishments where the chemical is used, the makeup of the worker population in these establishments and the diligence of employers in implementing workplace controls. During problem formulation, EPA should elaborate on how these considerations will be applied for the 10 chemicals.

More generally, when considering occupational exposures, EPA needs to recognize and account for differences in levels of exposure, workplace practices and susceptibility that result in significant gradations in risk, even within a single workplace. In workplaces where chemicals and chemical products are used, exposures typically occur most intensely among a highly exposed subgroup, rather than uniformly across the population of workers. In a vehicle repair shop, for example, chemical-intensive tasks on brakes, engines, and drive-train components are performed by a subset of workers who experience high levels of exposure to aerosolized degreasing solvents, whereas other workers in the same shop who perform diagnostic or electrical work, for example, experience little or no exposure to these solvents. To effectively characterize the "conditions of use" among workers, EPA must account for the levels and duration of exposure—and therefore risk—that occurs within highly exposed subgroups as a consequence of actual workplace conditions, rather than relying on an "average" estimated exposure across a population of workers, based on an assumption of "intended" use.

IX. EPA SHOULD NOT EXCLUDE FROM THE 1,4-DIOXANE EVALUATION ITS PRODUCTION AS A BYPRODUCT OR IMPURITY, WHICH IS A SIGNIFICANT SOURCE OF CONTAMINATION OF WATER SOURCES

The scoping document for 1,4-dioxane takes the unusual approach of precluding any consideration of this substance's manufacture as a byproduct or impurity in EPA's risk evaluation:

> "In the case of 1,4-dioxane, EPA anticipates that production of 1,4-dioxane as a by-product from ethoxylation of other chemicals and presence as a contaminant in industrial, commercial and consumer products will be excluded from the scope of the risk evaluation. These 1,4-dioxane activities will be considered in the scope of the risk evaluation for ethoxylated chemicals. EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane"[29]

This is a deeply flawed approach that will weaken the 1,4-dioxane risk evaluation and result in inadequate risk reduction during any subsequent rulemaking under section 6(a).

1,4-dioxane is a probable carcinogen that has contaminated drinking water and groundwater in multiple parts of the country, eliciting expressions of concern from many public officials and communities. A recent analysis of data from EPA-mandated monitoring indicates that water supplies for more than 7

[29] Scope of the Risk Evaluation for 1,4-Dioxane, at 8 (June 2017)

million Americans in 27 states contain 1,4-dioxane at levels above those that EPA and other agencies believe present an acceptable cancer risk.[30]

1,4-dioxane's presence in drinking water and groundwater is linked to several pathways of release into the environment. In addition to its manufacture as a chemical product, 1,4-dioxane is a byproduct of plastic production and other chemical manufacturing processes utilizing ethoxylation. Due to its production as a byproduct, it is present as an impurity in several industrial, commercial and consumer products. 1,4-dioxane often is found in the wastewater discharged by industrial facilities and POTWs. Its presence in wastewater is likely attributable not only to intentional production and use activities but to the use and disposal of products in which it is present as an impurity.

If 1,4-dioxane's manufacture as a byproduct and presence in products and waste streams as an impurity are excluded from EPA's risk evaluation, it will have no basis for accounting for these sources of environmental release and will be unable to characterize their contribution to levels of the chemical found in drinking water, surface water and ground water. This will make its assessment of the extent and causes of water contamination incomplete and undermine its ability to conduct an informed evaluation of the options for reducing contamination and risk. Any action it later decides to take under section 6 will thus be based on inadequate information and analysis and, as a result, may be ineffective and under-protective.

Manufacture as a byproduct is plainly within the definition of "conditions of use" in section 3(4) of TSCA. There is no basis in this provision or other parts of the law for differentiating between manufacture as a byproduct and purposeful production and including one in a risk evaluation but excluding the other. And in this instance, there's no evidence (and EPA does not claim) that exposure to and release of 1,4-dioxane as a byproduct and impurity are inconsequential from a risk standpoint.[31]

While EPA suggests that it might be more efficient or effective to address byproduct production of 1,4-dioxane in a separate section 6(a) rulemaking for ethoxylated chemicals, this seems far-fetched. If EPA assesses the contribution of these chemicals to 1,4-dioxane water contamination in the current risk evaluation, it will have a sound basis to regulate their production and use under section 6(a) if they are found to present an unreasonable risk of injury.[32] Otherwise, there is no telling when EPA might mitigate water contamination resulting from byproduct production of 1,4-dioxane production. Thus far, EPA has offered no indication when, if ever, it will make a high-priority designation for ethoxylated chemicals and assess their contribution to the presence of 1,4-dioxane in the environment.

We recommend that during problem formulation, EPA add 1,4-dioxane production as a byproduct and impurity to the scope of its risk evaluation.

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[30] Environmental Working Group, HIDDEN CARCINOGEN TAINTS TAP WATER, CONSUMER PRODUCTS NATIONWIDE (September 2017).

[31] Under our interpretation of section 6(b), EPA could not exclude a condition of use from the risk evaluation scope based on low risk in any event.

[32] Section 6(a) does not limit EPA to regulating purposeful production of a chemical subject to a risk evaluation. It can regulate production by other means so long as it has been assessed in that evaluation and found to present an unreasonable risk.

X. BASED ON THE GENERAL PRINCIPLES OUTLINED ABOVE AND OTHER GAPS IN ITS SCOPING DOCUMENTS, EPA SHOULD AUGMENT THESE DOCUMENTS IN SEVERAL SPECIFIC RESPECTS DURING PROBLEM FORMULATION

Applying the general approaches outlined in these comments and in light of several omissions we identified in individual scoping documents, we recommend that EPA bolster those documents during problem formulation as follows:

1-Bromopropane (nPB)

- In our initial comments to EPA, we specifically identified nPB as being imported by companies whose primary business is supplying the cosmetics industry.[33] While the EPA has noted that authorities such as the State of California have included nPB on lists of chemicals banned in cosmetics, the potential for nPB directly or indirectly (through residues remaining from cleaning manufacturing equipment) to be present in cosmetic products is not addressed as a potential use for further assessment.
- As discussed in detail in Part V of these comments, EPA failed to address the ozone depletion potential of nPB.
- While the scoping document includes references to those exposed to nPB from use of the chemical in consumer products, as well as those co-located with dry cleaning facilities utilizing the chemical, it does not clearly identify people who may be further exposed from chemical residuals, such as those wearing clothing cleaned with nPB or their children. This pathway is not discussed, even though the scoping document for PERC includes it from the similar use of PERC in dry cleaning.

Asbestos

- EPA's scoping document claims that public comments were not received on various imported asbestos containing products available in the United States: "Products available from several online retailers and distributers include brake blocks, aftermarket friction products, roof and non-roof coatings, and gaskets, most of which are imported. No public comments were received regarding these uses." However, we submitted detailed comments highlighting all of these items and more, including other building products. [34]
- EPA's failure to include a lengthy list of legacy uses, as further discussed in Part IV of these comments, is especially problematic for asbestos which was extensively sold and distributed and remains widely present and in use in our buildings and cities.
- The recycling of legacy materials, notably asphalt shingles containing asbestos, is a unique and ongoing use of the substance, and in particular is worthy of additional consideration by the EPA, as discussed in our initial comments.[35]

[33] EPA-HQ-OPPT-2016-0741-0027 at PDF Pages 25, 27, 31.
[34] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 19, 25-27
[35] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 21-22

- There is evidence that asbestos has been present in significant levels in some talc products as the result of colocation of asbestos and talc deposits, as we discussed in our initial comments.[36] This use and ongoing exposure are not addressed in the scoping document.

- The scoping document fails to look at the risks of exposure to those who are upstream to the process of utilizing asbestos in chlor-alkali processing. This would include miners and packaging workers (who, while likely abroad, are still being exposed as a result of the substance's uses in the US considered by the EPA), as well as transportation workers, first responders, and community members who may be exposed in the shipment and transfer of asbestos to the chlor-alkali facilities.

- The absence in the scoping document of total import volumes for asbestos is troubling because it deprives the public of an understanding of the aggregate quantities of asbestos present in the US. In fact, the Asbestos Disease Awareness Organization, along with the Environmental Working Group, released a statement on September 19 that, based on data from the Department of Commerce and US International Trade Commission, 705 metric tons of raw asbestos were imported in 2016, compared to 343 metric tons in 2015. This significant increase in imports is important information that should be given prominence in the problem formulation document for asbestos.

Carbon Tetrachloride (CTC)

- As discussed in detail in Part V of these comments, EPA failed to address the ozone depletion potential and global warming potential of CTC in its scoping document. This is particularly problematic for CTC, as its use as a feedstock or intermediary was exempted from the Montreal Protocol on the false assumption that CTC production would be phased out. In actuality, CTC production is poised for an increase due to its use in HFO manufacture, as we discussed on our initial comments.[37]

- As discussed in detail in Part III of these comments, EPA failed to describe with any specificity how it will look at aggregate and cumulative exposures. In the CTC scoping document, EPA seems to specifically discredit the need for this consideration. The Agency highlights the fact that some individuals may be exposed to CTC through vapor intrusion of ground sources of CTC into their home, but then states that, ". . . this route is not likely to be significant given the agency's identified conditions of use . . ." Clearly, whether the CTC inhaled by a resident is from the vapor intrusion or from an adhesive product, they face potential health risks from it. The Agency must consider all uses and sources of exposure in the risk evaluation in order to accurately assess the human health risk and fulfill its statutory obligations.

Cyclic Aliphatic Bromides Cluster (HBCD)

- As detailed in Part IV of these comments, EPA must not exclude the ongoing use and disposal from past introduction of HBCD in a variety of products. Significant exposures will continue to occur as products incorporating HBCD move through their lifecycle, and these exposures must be considered in the risk evaluation.

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[36] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 18-19

[37] EPA-HQ-OPPT-2016-0733-0023 at PDF pages 4-5, 19

N-Methylpyrrolidone (NMP)

- As we documented in our initial comments to the EPA, NMP has been used in the manufacturing of coating for the insides of aluminum spray cans.[38] Even products not including deliberate addition of NMP may therefore be contaminated with NMP, and this exposure pathway should be considered by the Agency.

- As detailed in Part II of these comments, EPA failed to provide specifics on susceptible subpopulations. While the Agency acknowledges that reproductive effects are to be assessed, considering the well-documented reproductive toxicity of NMP, the Agency needs to better detail how the risks to women of childbearing age will be addressed.

Methylene Chloride (MC)

- While the scoping document includes a use categorization for "other consumer products" including novelty "Drinking Bird" items, we identified an additional item,[39] a "Novelty Christmas Bubbling Night Light" labeled as containing MC but not previously included in EPA's "Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Methylene Chloride." These consumer-oriented uses that are attractive to children illustrate the need to be comprehensive in the determination of "reasonably foreseeable" uses.

XI. EPA MAY NOT PREJUDGE THE ABSENCE OF ADVERSE EFFECTS FOR PARTICULAR END-POINTS AT THE SCOPING STAGE AND SHOULD DEFER SUCH CONCLUSIONS UNTIL THE SYSTEMATIC REVIEW STAGE OF ITS RISK EVALUATION

In some scoping documents, EPA has decided that the subject chemical does not raise concerns for particular endpoints and, therefore, it will not address these end-points in its risk evaluation. Examples are given in the table below where EPA concludes that HBCD, NMP and pigment violet 29 are not genotoxic:

Chemical	Example Text from EPA Scoping Document
HBCD	"Available data suggest that HBCD is not genotoxic. Existing assessments have also concluded, based on genotoxicity information and a limited lifetime study, that HBCD is not carcinogenic (NICNAS, 2012; EINECS, 2008; TemaNord, 2008; OECD, 2007). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity or cancer hazards in the risk evaluation of HBCD at this time."[40]
NMP	"NMP is not mutagenic, based on results from bacterial and mammalian *in vitro* tests and *in vivo* systems and is not considered to be carcinogenic (RIVM, 2013; OECD, 2007; WHO, 2001). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity and cancer hazards in the NMP risk evaluation."[41]

[38] EPA-HQ-OPPT-2016-0743-0031 at PDF page 18
[39] https://www.amazon.com/Bubble-Nightlight-Novelty-Christmas-Bubbling/dp/B00PV61HXC/
[40] EPA, *Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster, June 2017, at.* 36
[41] EPA, *Scope of the Risk Evaluation for N-Methylpyrrolidone,* June 2017, *at* 36

Pigment violet 29	"Testing for carcinogenicity of Pigment Violet 29 has not been conducted. However, negative genotoxicity results, structure-activity considerations and the expectation of negligible absorption and uptake of Pigment Violet 29 (based on very low solubility), indicate carcinogenicity of Pigment Violet 29 is unlikely. Unless new information indicates otherwise, EPA does not expect to conduct additional, in-depth analyses of genotoxicity and cancer hazards in the risk evaluation of Pigment Violet 29."[42]

EPA cannot reach such definitive conclusions at the scoping stage. The required course under the law is to proceed with a systematic review of the relevant data (a process that EPA strongly endorses) and withhold any conclusions about particular end-points until this review is complete.

In the case of HBCD, for example, a more thorough review would reveal two recent studies indicating carcinogenic potential. One suggests that HBCD could "enhance progression of prostate cancer by modulating growth and migration of LNCaP prostate cells,"[43] and the other concludes the genotoxicity of HBCD is dose-dependent and related to DNA repair.[44] These new studies are examples of the need for EPA to assure that it has fully considered all the available data through the systematic review process in order to avoid premature and possibly incorrect decisions to drop particular end-points at the scoping stage.

XII. PROBLEM FORMULATIONS SHOULD HIGHLIGHT ASPECTS OF USE AND EXPOSURE WHERE AVAILABLE INFORMATION IS INSUFFICIENT AND REQUEST OR REQUIRE SUBMISSION OF THIS INFORMATION BY INDUSTRY

Our own research on the 10 chemicals and the scoping documents themselves confirm that there are significant gaps in the use and exposure information available to EPA and that they will weaken the quality of EPA's risk evaluations unless filled. Although the timeframe for completing risk evaluations is compressed, there is still a window for augmenting the information-base used to conduct them. To take advantage of this opportunity, EPA should include in each problem formulation document a description of information on use and exposure that is lacking and a request that industry and other interested parties submit or obtain that information as expeditiously as possible.

EPA should also signal its readiness to use its mandatory information collection authorities under TSCA to fill data-gaps where voluntary submissions are not timely or adequate. The LCSA expands these authorities and streamlines the process for exercising them, removing the barriers to information development that hamstrung EPA under the old law. For example, section 4 now authorizes EPA to issue orders where necessary to "perform a risk evaluation." Such orders can be used to require industry to develop new information on the frequency, levels and duration of exposure for a chemical's conditions of use. Alternatively, EPA can use its subpoena authority under section 11 to obtain such information that already exists but has not been provided to EPA. EPA should specify in the problem formulation document its roadmap and timetable for filling data gaps using these authorities.

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[42] EPA, *Scope of the Risk Evaluation for Pigment Violet 29*, June 2017, at 29.

[43] Seung-Hee Kim, et al, 2016. Influence of hexabromocyclododecane and 4-nonylphenol on the regulation of cell growth, apoptosis and migration in prostatic cancer cells. Toxicology in Vitro. 32:240-247. April 2016.

[44] Rui Jing Li, et al. Hexabromocyclododecane-induced Genotoxicity in Cultured Human Breast Cells through DNA Damage. Letter to Editor. Biomedical and Environmental Sciences. 30(4): 296-300.

Where the database available for a risk evaluation is incomplete, it is critically important that EPA not equate the absence of data with the absence of risk. For example, if EPA lacks data to assess a chemical's carcinogenicity, its risk evaluation needs to clearly state that cancer risk has not been addressed, that the chemical may or may not present such a risk, and that this end-point is outside the scope of its evaluation because of the absence of data. EPA should make the same disclaimers for conditions of use that cannot be adequately characterized, even by using default assumptions or extrapolation methods, because basic information about the nature of the use and scope and extent of exposure is unavailable.

XIII. EPA NEEDS TO LIMIT REDACTION FROM SCOPING AND PROBLEM FORMULATION DOCUMENTS OF CRITICAL INFORMATION CLAIMED CBI SO THAT TRANSPARENCY AND PUBLIC PARTICIPATION IN THE RISK EVALUATION PROCESS ARE NOT IMPAIRED

The scoping documents omit critical exposure and use information that has been claimed as confidential business information (CBI) that must be withheld from disclosure under TSCA. In some cases, the information is as basic as the total volume of the chemical manufactured and imported in the US. For example, the scoping documents fail to provide total manufacture/import volumes for asbestos, HBCD and pigment violet 29. Not only is this information obtainable in the public domain but it is fundamental to public understanding of the risks posed by these chemicals and, therefore, to informed public participation in the risk evaluation process.[45]

During problem formulation, EPA should make a concerted effort to limit the redaction of CBI-claimed production, use and exposure data that are essential for the transparency of the risk evaluation process. Several tools can be used for this purpose.

First, section 14(b)(3) of TSCA declares that "information not protected from disclosure" includes:

> "any general information describing the manufacturing volumes, expressed as specific aggregated volumes or . . . expressed in ranges."
>
> "a general description of a process used in the manufacture or processing and industrial, commercial or consumer functions and uses of a chemical, substance, mixture or article containing a chemical substance or mixture . . ."

This provision compels the disclosure of much of the information in scoping documents claimed CBI.

Alternatively, section 14(d)(7) provides that the Administrator may disclose information otherwise warranting CBI protection if he or she "determines that disclosure is relevant in a proceeding under this Act." The risk evaluations that EPA is conducting on the 10 chemicals under section 6(b)(2)(A) of TSCA represent a "proceeding" under TSCA. Information submitted by industry on the 10 chemicals is plainly "relevant" to these evaluations because it will inform how EPA assesses exposures and related risks

[45] For asbestos, SCHF and Environmental Health Strategy Center were able to use US government data accessible through the Panjiva database to determine annual asbestos imports over an extended period. As noted above, a more recent analysis of import data by the Asbestos Disease Awareness Organization shows that asbestos imports doubled in 2016, a startling finding that should be central to EPA's risk evaluation because of its implications for exposure to asbestos in the US.

associated with manufacture, processing and downstream commercial and consumer use. Thus, EPA can and should decide to disclose all information on the 10 chemicals notwithstanding any CBI claims.

Finally, to the extent these grounds for disclosure do not apply, EPA should use its authority under section 14(f)(1)(C) to require immediate substantiation of CBI claims for information for which "disclosure would be important to assist the Administrator in conducting risk evaluations . . . under section 6." This provision should be applied broadly to accomplish disclosure of all information that would be of value to the public in commenting on risk evaluations.

CONCLUSION

Our groups appreciate the opportunity to comment on the 10 scoping documents and look forward to continued dialogue with the Agency as it develops problem formulation documents and proceeds with risk evaluations on the 10 chemicals.

If you have any questions, please contact SCHF counsel, Bob Sussman, at bobsussman1@comcast.net or 202-716-0118.

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Comparison of NTP OHAT and USEPA TSCA Study Quality Criteria — Trichloroethylene (TCE) and Congenital Heart Defects (CHDs) as a Case Study

ToxStrategies

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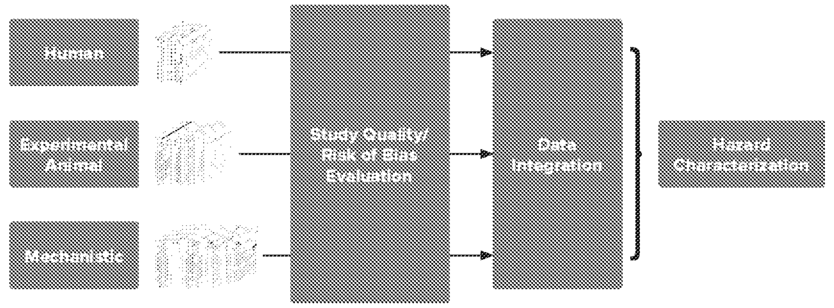


Introduction

- Current TCE regulations are based on a single experimental animal study reporting an association between gestational exposure to trichloroethylene (TCE) and the development of congenital heart defects (CHDs) in offspring. This TCE-CHD association is controversial as it was not observed in the 11 other TCE developmental animal toxicology studies, including GLP studies specifically designed to repeat the single study that reported an association.
- Globally, systematic review is being implemented to facilitate hazard and risk evaluations. As part of developing best practices, various critical appraisal tools are being designed or refined to accommodate evidence bases which include many different types of studies (i.e., experimental animal, *in vitro*, and observational studies).
- Existing critical appraisal tools generally assess the internal validity of a study, as assessed by the risk of bias (RoB). With increasing use in toxicology, it is being recognized that other aspects of study quality are important on the individual study level (e.g., external validity or relevance). Some such aspects are considered in a newly released study quality tool issued by the USEPA-OPPT to facilitate the TSCA risk assessment systematic review process (USEPA, 2018). This tool is unique as it includes study quality metrics for mechanistic studies (e.g., *in vitro* studies).
- To date, only subsets of the TCE-CHD literature (human, animal) have been subjected to formal systematic critical appraisal (Wikoff et al., 2018).

Objective

To assess the impact of various systematic critical appraisal tools in the evaluation of the full evidence base (human, animal, and mechanistic data) for TCE-CHD.

Methods

Development of TCE-CHD Evidence Base (Literature Search):

- Using ad hoc searching and reference chasing, epidemiology, animal toxicology, and mechanistic studies were identified from recent comprehensive reviews conducted systematically (Makris et al., 2016; Wikoff et al., 2018). Additional PubMed and Embase searches were also conducted using the same search syntax utilized to capture relevant studies published since Wikoff et al. (2018). Searches were executed October 30, 2018.
- Mechanistic studies were categorized based on the assay type(s) to accommodate the TSCA study quality tool: *in vivo* (animals exposed), *in vitro* (cell culture, *in ovo*, *ex ovo*, *ex vivo*).

Critical Appraisal Tools (Table 1)

- **OHAT RoB:** Two study categories (animal and human) with defined, and reviewer refined, criteria for assessing bias (low, high; definite, probable). The RoB for the TCE-CHD human and animal literature is based on Wikoff et al. (2018).
- **TSCA Study Quality Evaluation:** Three study categories (human, *in vivo*, and *in vitro*) with specific evaluation and scoring metrics, each metric being scored on 1 of 4 criteria; overall study quality was determined by weighted scoring calculations and categorizations.
- **SciRAP:** Used in this effort to compare TSCA *in vitro* study quality results. Criteria evaluate the reporting and methodological quality, and relevance of *in vivo* and *in vitro* studies. Tool calculates a score for each category based on reviewer selection of several criteria.

Study Quality Assessment Procedure

- Pilot assessments: Independent review of subset of studies/experiments by two analysts for each of the three study categories. Decisions, interpretations, and refinements were documented.
- Quality assessments were conducted by two scientists with experience reviewing epidemiology (MS, JB), experimental animal (SF, JU), and mechanistic (GC, JU) studies. In cases of conflict, a third scientist (DW) was consulted to facilitate a consensus solution.

Data Integration and Body of Evidence Assessment

- Integration approach is based on OHAT (2015) and builds on that from Wikoff et al. (2018) to include mechanistic data and consider data quality output as determined by various appraisal tools.
- For mechanistic data, confidence-rating factors proposed by OHAT (2015) were considered: magnitude/potency, dose-response, consistency, directness, validity. Consideration was also given to the biological plausibility of data in the context of an adverse outcome pathway construct (which also relies on data from animal and human evidence streams to characterize adverse outcomes; in the case of TCE-CHD, adverse outcomes are limited as the majority of data suggest lack of such).

Table 1. Critical Appraisal Tool Study Quality Domains/Metrics

Study Type	NTP-OHAT RoB (2015)	USEPA OPPT TSCA (2018)	SciRAP (2018)
Epidemiology	**7 Questions covering 6 Bias Domains:** 1. Selection Bias (1) 2. Confounding Bias (1) 3. Attrition/Exclusion Bias (1) 4. Detection Bias (2) 5. Selective Reporting (1) 6. Other Bias (1 - covers statistics)	**15 Metrics covering 5 Study Elements:** 1. Study Participation (3) 2. Exposure Characerization (3) 3. Outcome Assessment (2) 4. Potential Counfounding/Variable Control (3) 5. Analysis (4)	[Not covered]
Animal Toxicology	**9 Questions covering 6 Bias Domains:*** 1. Selection Bias (2) 2. Performance Bias (2) 3. Attrition/Exclusion Bias (1) 4. Detection Bias (2) 5. Selective Reporting (1) 6. Other Bias (1 - covers statistics)	**24 Metrics covering 7 Study Elements:** 1. Test Substance (3) 2. Test Design (3) 3. Exposure Characterization (6) 4. Test Organism/Test Model (3) 5. Outcome Assessment (5) 6. Confounding/Variable Control (2) 7. Data Presentation and Analysis (2)	**53 Criteria covering 3 Study Elements:** 1. Reporting Quality (30) 2. Methodological Quality (18) 3. Relevance (5) [Not utilized in the current effort]
In vitro	[Not covered]	**25 Metrics covering 7 Study Elements:** 1. Test Substance (3) 2. Test Design (4) 3. Exposure Characterization (6) 4. Test Model (2) 5. Outcome Assessment (4) 6. Confounding/Variable Control (2) 7. Data Presentation and Analysis (4)	**42 Criteria covering 3 Study Elements:** 1. Reporting Quality (23) 2. Methodological Quality (15) 3. Relevance (4)

* OHAT RoB guidelines encourages reviewers to expand/modify/split questions to make relevant to PECO. For TCE-CHD case study, Wikoff et al. (2018) split 9 animal questions out to 14 questions.

Results

TCE-CHD Evidence Base

Table 2. TCE-CHD Literature

Study Type	# Relevant Published Studies	# Study Quality Assessments	
Epidemiology	10	9	
Animal Toxicology	11	12	
Mechanistic	22	Total: 68 [Avg: 3.1 Assays/Study]	
		In vivo: 5 In vitro (cell culture): 26 In vitro (in ovo): 21 In vitro (ex ovo): 3	In vitro (ex vivo): 7 In vitro (zebrafish): 5 Unknown model: 1
Total	**43**	**89**	

Critical Appraisal of Epidemiological Data

- Overall study quality as assessed by the various tools was low for the epidemiological literature. Appraisal outcome was driven by limitations in study design and reporting particularly related to study participation, exposure assessment, and confounding.
- **Conclusion:** The nine studies comprising the human evidence base for TCE-CHD are of very limited study quality for risk assessment.

Table 3. Critical Appraisal of Human Studies Relevant to TCE-CHD Risk Assessment

Reference	Study Design	TSCA designation[1]	OHAT RoB Designation[2]
Epidemiology Studies			
Bove et al. (1995)/Bove (1996)	Cross-sectional (assumed exposure via public water)	Unacceptable (2x "4" scores)	Tier II
Brender et al. (2014)	Case-control (assumed exposure via air)	Unacceptable (1x "4" scores)	Tier II
Forand et al. (2012)	Ecological/Cross-sectional (assumed exposure via air)	High Quality (score=1.5)	Tier II
Gilboa et al. (2012)	Case-control (assumed exposure via air)	Unacceptable (1x "4" scores)	Tier II
Goldberg et al. (1990)	Pseudo-case-control (assumed exposure via public water)	Unacceptable (3x "4" scores)	Tier III
Lagakos et al. (1986)	Cross sectional (assumed exposure via public water)	Unacceptable (6x "4" scores)	Tier II
Ruckart et al. (2013)	Case-control (assumed exposure via public water)	Unacceptable (3x "4" scores)	Tier III
Tola et al. (1980)	Cohort (assumed exposure via air)	Unacceptable (9x "4" scores)	Tier II
Yauck et al. (2004)	Case-control (assumed exposure via air)	Unacceptable (4x "4" scores)	Tier II

[1] For OPPT scores, "high quality" studies <1.7, "medium quality" studies <2.3 and ≥1.7, "low quality" studies ≥2.3; any study with at least one metric score = 4 is automatically of "unacceptable quality".
[2] OHAT RoB Tiers as evaluated and reported in Wikoff et al. (2018)

Critical Appraisal of Experimental Animal Data

- Overall study quality as assessed by the various tools was medium to high for the experimental animal research. Appraisal outcome was largely driven by well reported and appropriate study design, consistent experimental conditions, and valid outcome methodologies.
- The Dawson et al. (1993)/Johnson et al. (2003) rat drinking water study was characterized as unreliable (poor study quality; high internal bias) by both OHAT and TSCA tools; common issues related to lack of concurrent controls, multiple vehicles within study groups, and unvalidated outcome assessment method.
- **Conclusion:** The majority of the animal evidence base for TCE-CHD [sans Dawson et al. (1993)/Johnson et al. (2003)] are amenable for risk assessment.

Table 4. Critical Appraisal of Animal Toxicology Studies Relevant to TCE-CHD Risk Assessment

Reference	Study Design	TSCA designation[1]	OHAT RoB Designation[2]
Oral Studies			
Cosby and Dukelow (1992)	Mouse - oral gavage GD 1-5, 6-10, or 11-15	Medium Quality (score=2.1)	Tier II
Dawson et al. (1993)/Johnson et al. (2003)	Rat - drinking water GD 1-22	Unacceptable (2x "4" scores)	Tier III
Fisher et al. (2001)	Rat - oral gavage GD 6-15	High Quality (score=1.5)	Tier II
Narotsky and Kavlock (1995)	Rat - oral gavage GD 6-19	Medium Quality (score=1.9)	Tier II
Narotsky et al. (1995)	Rat - oral gavage GD 6-15	Medium Quality (score=1.9)	Tier II
Inhalation Studies			
Carney et al. (2006)	Rat - whole body 6 hr/d, GD 6-20	High Quality (score=1.4)	Tier I
Dorfmueller et al. (1979)	Rat - whole body 6 hr/d, GD 1-20	Medium Quality (score=1.8)	Tier I
Hardin et al. (1981)a	Rat - whole body 7 hr/d, GD 1-19	High Quality (score=1.4)	Tier II
Hardin et al. (1981)b	Rabbit - whole body 7 hr/d, GD 1-22	High Quality (score=1.4)	Tier II
Healy et al. (1982)	Rat - whole body 4 hr/d, GD 8-21	Medium Quality (score=2.0)	Tier II
Schwetz et al. (1975)a	Rat - whole body 7 hr/d, GD 6-15	Medium Quality (score=1.8)	Tier I
Schwetz et al. (1975)b	Mouse - whole body 7 hr/d, GD 6-15	Medium Quality (score=1.8)	Tier I

[1] For OPPT scores, "high quality" studies <1.7, "medium quality" studies <2.3 and ≥1.7, "low quality" studies ≥2.3; any study with at least one metric score = 4 is automatically of "unacceptable quality".
[2] OHAT RoB Tiers as evaluated and reported in Wikoff et al. (2018)

Critical Appraisal of Mechanistic Datasets

- Pilot study of 10 experimental datasets using TSCA demonstrated that five study metrics commonly differentiated studies; these were defined as "Key Metrics." (**Table 5**)
- Quality rankings based on the TSCA tool varied by study model (**Figure 1**).
- Aspects that commonly differentiated studies within the TSCA tool included reporting on the preparation and storage of the test substance (Metric 8), elements of data analysis (Metrics 22 and/or 23), and reporting on cytotoxicity (Metric 24, only relevant to cell culture experiments) (**Figure 2**).
- Study quality categorizations were overall similar for the subset of experiments also assessed using SciRAP (**Table 6**).
- **Conclusion:** The majority of the mechanistic studies are not reliable for risk assessment. Traditional assessment parameters (e.g., magnitude, consistency) were not sufficient to facilitate conclusions for mechanistic data. Consideration of the type of outcome assessed (e.g., gene expression, *in ovo* development), the study model (e.g., chicken eggs, rat whole culture embryos, zebrafish larvae, human embryonic stem cells), as well as the plausibility of findings in a biological construct (e.g., adverse outcome pathway type of construct) were critical to integrating the evidence. The few mechanistic studies that were of sufficient quality were limited in their applicability due to heterogeneous models of questionable relevance to human physiology and exposure timing/dosing. Furthermore, the outcomes from these remaining studies were also inconsistent as it relates to outcome observations in mammalian species.

Table 5. Key Metrics Identified using TSCA Study Quality Metrics for TCE-CHD In Vitro Experiments

Metric No.	Metric Title	Metric Description
8	Preparation and Storage of Test Substance	Did the study characterize preparation of the test substance and storage conditions? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability and solubility (if applicable)?
11	Exposure Duration	Was the exposure duration (e.g., minutes, hours, days) reported and appropriate for this study type and/or outcome(s) of interest?
16	Outcome Assessment Methodology	Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints and timing of assessment) sensitive for the outcome(s) of interest (e.g., measured endpoints that are able to detect a true effect)?
22	Data Analysis	Were statistical methods, calculations methods, and/or data manipulation clearly described and appropriate for dataset(s)?
24	Cytotoxicity	Were cytotoxicity endpoints defined, if necessitated by study type, and were methods for measuring cytotoxicity described and commonly used for assessments?

Figure 1. TCE-CHD Mechanistic Studies by Model Type and Study Quality Category Based on TSCA Systematic Review Guidelines

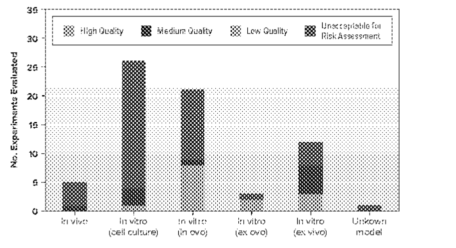


Figure 2. TSCA Study Quality Metrics Scored "Unacceptable" Across TCE-CHD Mechanistic Evidence Base

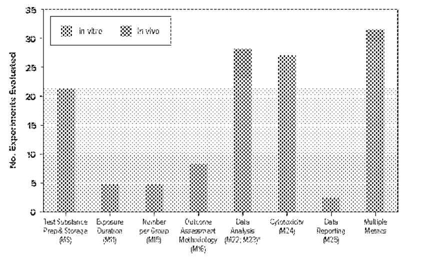
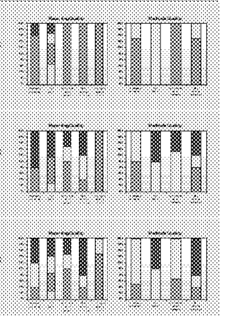


Table 6. Comparison of In Vitro Study Quality Evaluation Tools

Study	Exposure Model & Endpoint	Study Quality Evaluation Outcome: TSCA	Study Quality Evaluation Outcome: SciRAP
Drake et al EHP (2006)	In ovo: Level of apoptosis in atrioventricular cushion and outflow tract sections of HH24 staged chick embryo hearts	**Score:** 1.5 **Interpretation:** High Quality Study **Consequence:** Retain in TCE-CHD evidence base for risk assessment	**Reporting Quality Score:** 78 out of 100 **Methodological Quality Score:** 85 out of 100 **Consequence:** None defined
Harris et al (2018)	In vitro: Protein activity in transformed human liver cell line	**Score:** Not calculated; multiple metrics scored =4 **Interpretation:** Unacceptable for risk assessment **Consequence:** Remove from evidence base for TCE-CHD risk assessment	**Reporting Quality Score:** 50 out of 100 **Methodological Quality Score:** 50 out of 100 **Consequence:** None defined
Selmin et al (2005)	In vitro: Gene transcription levels in transformed rat heart cell line	**Score:** Not calculated; multiple metrics scored =4 **Interpretation:** Unacceptable for risk assessment **Consequence:** Remove from evidence base for TCE-CHD risk assessment	**Reporting Quality Score:** 43 out of 100 **Methodological Quality Score:** 46 out of 100 **Consequence:** None defined



Body of Evidence Assessment

- Overall, there is higher confidence in the animal studies compared to human studies or mechanistic studies, based on the output of the various critical appraisal tools.
  1. Notably, the Dawson et al. (1993)/Johnson et al. (2003) study was determined to be unreliable by both appraisal tools. This emphasizes the likelihood that shortcomings in methodological and reporting aspects can explain the inconsistent findings of this study relative to the other 11 animal studies in the evidence base.
- Data Integration (**Figure 3**): Considered together, the available human, animal, and mechanistic study data support a lack of association between gestational TCE exposure and CHDs.
  1. Human studies → Low confidence in evidence stream associating in utero TCE exposure with increased risk of CHDs (similar to conclusions using OHAT RoB tool): Only a single study met TSCA quality criteria, and that was an ecological study.
  2. Animal studies → High confidence in evidence stream for TCE-CHD null hypothesis (i.e., no association of gestational TCE exposure and increased CHD risk): Only study to show dose response effect failed to meet TSCA study quality criteria.
  3. Mechanistic studies → Low confidence in evidence stream: inconsistency and relevance of outcomes and non-mammalian models are difficult to interpret given the lack of effect in experimental animal models (mammalian).

Figure 3. Data Integration: Evidence Stream Summaries and Integrated Conclusion

Conclusions and Confidence By Stream: Human Data	Animal Data	Mechanistic Data	Integrated Conclusion
Low to very low (inadequate) confidence to determine the potential for, or the direction of, an effect	+ Very high level of confidence supporting lack of association between TCE exposure (oral and inhalation) and CHD Single inconsistency explained by methological and reporting limitations*	+ Low confidence in the body of evidence to characterize CHD or mechanistic events potentially associated with CHD Complex interpretation given inconsistinecy in findings relative to other streams and limitations in relevance of non mammalian study models combined with limitations in study quality	→ Available evidence support a lack of association between gestational TCE exposure and CHD in humans

Conclusions

- Despite differences in the critical appraisal tools employed herein, consideration of study quality resulted in similar findings: the experimental animal studies offer the highest level of confidence. Both approaches deemed the Johnson et al. (2003) rat study unreliable for using in quantitative risk assessment.
- Given the consistent findings of experimental animal studies demonstrating a lack of TCE-CHD relationship, the utility of assessing and integrating the mechanistic data is limited, particularly considering the complexity of interpreting the relevance of diverse models (e.g., non-mammalian) and exposure paradigms (e.g., direct *in vitro* cell culture exposures extrapolate to high exposure concentrations in humans) utilized in a risk assessment context. Notably, in contrast to the rodent data, non-mammalian models (*in ovo*, zebrafish) provide the strongest evidence supporting TCE-CHD association. These models are heuristic tools useful for hypothesis development but are of highly questionable relevance for human health risk assessment.
- The use of multiple tools for evaluating the quality of study data across evidence bases can increase confidence in systematic review findings and provide an understanding of the practical application of available approaches.

Acknowledgements This work was funded by the American Chemistry Council.

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Environmental Defense Fund Comments on

Ten Scopes under the Toxic Substances Control Act

Docket IDs: EPA-HQ-OPPT-2016-0725 (Pigment Violet 29), EPA-HQ-OPPT-2016-0723 (1-4, Dioxane), EPA-HQ-OPPT-2016-0732 (Tetrachloroethylene), EPA-HQ-OPPT-2016-0733 (Carbon Tetrachloride), EPA-HQ-OPPT-2016-0735 (HBCD), EPA-HQ-OPPT-2016-0736 (Asbestos), EPA-HQ-OPPT-2016-0737 (Trichloroethylene), EPA-HQ-OPPT-2016-0741 (1-Bromopropane), EPA-HQ-OPPT-2016-0742 (Methylene Chloride), and EPA-HQ-OPPT-2016-0743 (N-Methylpyrrolidone)

Submitted Tuesday September 19, 2017

The Environmental Defense Fund (EDF) appreciates the opportunity to provide comments to the Environmental Protection Agency (EPA) on the scopes for the risk evaluations for the first ten chemicals being evaluated under section 6(b)(4) of the Toxic Substances Control Act (TSCA) as amended by the Lautenberg Act, enacted on June 22, 2016.

In addition to specific comments on each chemical, EDF is providing broad comments addressing the scopes of risk evaluations for the first 10 chemicals as well as others in the future. While our comments are broadly applicable to all of the scope documents, we include examples from specific scopes to illustrate flaws and limitations.

As explained below, these scopes deviate from certain requirements of the law and in places are too unclear and vague or ambiguous to allow us to provide definitive comments. EDF recognizes that EPA was working under tight deadlines in producing these scopes – a problem it further exacerbated by EPA's decision to make major, late changes to the risk evaluation rule. EPA should take advantage of the upcoming problem formulation stage to address the many problems we identify below, and to more clearly and transparently explain its plans for these risk evaluations.

Before discussing the merits of the scoping documents, EDF provides the following clarification about its citation approach. Each scoping document contains largely identical, boilerplate language providing the agency's overall legal approach to "conditions of use" as well as its approaches on some other issues. Indeed, each document includes the same typos or misquotes of the underlying law. For ease of reference and to reduce excessive citations, EDF quotes from the asbestos scoping document and provides simply the page number when addressing these broader legal problems that are present in each scoping document. These comments equally apply to all scoping documents since they all contain

this same language; the only difference is page number. When EDF is specifically quoting another scoping document, we provide a citation clarifying that point.

Contents:

I. TSCA requires EPA to analyze whether a chemical substance, as a whole, presents an unreasonable risk, and EPA does not have discretion to ignore conditions of use.

EPA's scoping documents (pp.11-13) state that EPA has determined that "certain activities may not generally be considered to be conditions of use" (p.11) and also that EPA may "exclude certain activities that EPA has determined to be conditions of use" (p.12). EPA's approach asserts that EPA is allowed to ignore numerous circumstances falling within the statutory definition of "conditions of use" and is contrary to law. For the current set of chemicals under review, EPA may well be ignoring circumstances leading to ongoing exposures, and as a result, will fail to evaluate the risks the chemicals actually pose to human health and the environment.

TSCA's language and structure unambiguously foreclose EPA's interpretation. EPA's decision to disregard certain uses and exposures is also "arbitrary, capricious, [or] an abuse of discretion" under the APA, 5 U.S.C. § 706(2)(A), because it will lead EPA to consider "factors which Congress has not intended it to consider [and] entirely fail[] to consider an important aspect of the problem." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Moreover, as the scoping documents themselves reveal, this approach leads to irrational and arbitrary applications. Instead, EPA should be guided by the statutory language and consider all of those circumstances falling within the definition of "conditions of use." EPA should evaluate all of the circumstances revealed by the evidence of use and exposure, not ignore evidence because of self-imposed blinders.

A. The plain text, overall structure, purpose, and legislative history of TSCA indicate that EPA has to determine whether a chemical substance presents an unreasonable risk comprehensively, under all of its conditions of use.

i) *The plain text requires EPA to consider all conditions of use.*

Statutory interpretation should begin, as always, with the language of the statute. The plain language of both the risk evaluation provision and the definition of conditions of use support the interpretation that EPA must consider all circumstances falling within the statutory definition of "conditions of use." The main risk evaluation provision, TSCA § 6(b)(4)(A), directs that EPA "shall conduct risk evaluations pursuant to this paragraph to determine whether a chemical substance presents an unreasonable risk *** under the conditions of use." 15 U.S.C. § 2605(b)(4)(A). Inserting the statutory definition of conditions of use, this provision provides that EPA "shall conduct risk evaluations pursuant to this paragraph to determine whether a chemical substance presents an unreasonable risk *** under "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." *Id.* §§ 2605(b)(4)(A), 2602(4). Thus, EPA has to analyze the risks of a substance under the circumstances described in the definition of "conditions of use," and no qualifying language allows EPA to exclude circumstances within that definition. The clause "as determined by the Administrator" calls for a factual finding or determination to be made by EPA. The relevant dictionary definition of "determine" is to "ascertain or establish exactly, typically as a result of research or calculation." OXFORD

AMERICAN DICTIONARY 474 (3d ed. 2010). While EPA may exercise reasonable judgment when interpreting "reasonably foreseen," nothing in this language grants EPA discretion to *ignore* factual circumstances that fall within the definition of "conditions of use." Indeed, statutes often direct agencies "to determine" things or make "determinations," and it is understood that the agency must make the finding required by the statutory language.

EPA's position that it can ignore known and foreseeable uses violates the text of the law. In the scoping documents, EPA asserts that it may ignore "legacy uses" and "associated disposals," impurities, alleged "de minimis" exposures, intermediates, conditions of use within closed systems, and conditions of use that have been analyzed by another regulatory agency (p.12). But "conditions of use" expressly includes "the circumstances *** under which a chemical substance is intended, known, or reasonably foreseen to be to be manufactured, processed, distributed in commerce, used, or disposed of." 15 U.S.C. § 2602(4). And every one of those circumstances is a "known" or "reasonably foreseen" "manufacture", "process[ing]," "use," or "disposal of" a chemical substance. Congress expressly chose to define "conditions of use" broadly to include not only "intended," but also "known" or "reasonably foreseen" manufacture, processing, distribution, use, and disposal. 15 U.S.C. § 2602(4). Disregarding chemical substances present as impurities or byproducts in the scoping documents, for example, because they are not "intended" essentially reads the other two scenarios out of the statute. Similarly, all the other identified conditions of use are also "intended, known, or reasonably foreseen." For example, EPA's scope suggests that 90% of the domestic production of Pigment Violet 29 "is processed as a site-limited intermediate." Pigment Violet 29, Scope at p.19, Docket ID: EPA-HQ-OPPT-2016-0725. It would absurd to ignore these intermediate uses when analyzing this chemical; doing so will lead to a truncated and incomplete analysis. Similarly the decision to exclude 1,4-dioxane's presence in numerous consumer, commercial, and industrial products as a byproduct of ethoxylation is entirely inappropriate, and will result in deficient and erroneous evaluation and determination of the chemical substance's risks. The same points can be made for many of the other chemicals used as intermediates or present as byproducts of chemical or product manufacture.

In contrast to the correct interpretation, EPA's new interpretation finds no support in the text. In the final risk evaluation rule (82 Fed. Reg. 33,726, 33,729 (July 20, 2017)), the only statutory textual basis for EPA's theory appears to be the "expects to consider" clause in the scope provision, TSCA § 6(b)(4)(D), requiring EPA to "publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations the Administrator *expects to consider*." 15 U.S.C. § 2605(b)(4)(D). But "expects to consider" does not mean "chooses to consider" or "prefers to consider." It is not the language of discretion; it is temporal language of anticipation or prediction. The dictionary definition of "to expect" is to "regard (something) as likely to happen." OXFORD AMERICAN DICTIONARY 609 (3d ed. 2010). This language indicates that, in the scope, EPA should describe what it anticipates studying, but it does not state that EPA has discretion to choose to ignore intended, known, or reasonably foreseen uses, hazards, or exposures. Moreover, the provision dictating what EPA must consider during a risk evaluation does not limit EPA's analysis to conditions of use identified in the scope. 15 U.S.C. § 2605(b)(4)(F). Indeed, EPA must consider all such conditions to fulfill its requirement that EPA account for the ''likely duration, intensity, frequency, and

number of exposures under the conditions, where relevant." 15 U.S.C. 2605(b)(4)(F)(iv). Thus, the statutory language does not support EPA's assertion of discretion, including EPA's decision to limit its analyses to those factors identified in each scope. For example, under the rule of the last antecedent, the phrase "the Administrator expects to consider" does not even *modify* "conditions of use" or "hazards" or "exposures." Notably, EPA has so little regard for the statutory language that it repeatedly misquotes this language in significant ways.

Textually, EPA's argument also directly conflicts with TSCA § 26(k). 15 U.S.C. § 2625(k). TSCA § 26(k) requires EPA to "take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available to the Administrator." *Id.* Notably, this requirement does not include *any* conditional phrase that modifies "conditions of use." And Congress included this provision to ensure that EPA could not ignore "reasonably available" "information relating to a chemical substance or mixture"; the purpose of this provision is to compel EPA to consider all reasonably available information. It would undermine this directive if EPA chooses to arbitrarily ignore certain uses and related exposures.

ii) *TSCA's overall structure requires EPA to consider all of the conditions of use.*

TSCA provisions direct EPA to prepare risk evaluations and the related findings for "chemical substances," *as a whole*, not for specific or limited conditions of use of those substances. For example, the risk management provision expressly requires EPA to address risks when the risks arise from combined exposure. TSCA § 6(a) provides that: "If [EPA] determines in accordance with [the risk evaluation provision] that the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, *or that any combination of such activities*, presents an unreasonable risk of injury to health or the environment," then EPA must issue a risk management rule. 15 U.S.C. § 2605(a); *see also* 15 U.S.C. § 2608(a) (using same language in provision governing requests to other federal agencies to address risks). Thus, if "any combination" of conditions of use presents an unreasonable risk, EPA must issue a risk management rule. But EPA must analyze *all* of these activities to assess whether *any combination* presents a risk.

When describing the end of a risk evaluation, TSCA requires EPA to make a finding about the "chemical substance" with no reference to conditions of use. *See, e.g.*, 15 U.S.C. § 2605(c)(1), (*i*) ("If the Administrator determines that a chemical substance presents an unreasonable risk of injury to health or the environment in accordance with subsection (b)(4)(A)," then EPA must issue a regulation to address the unreasonable risk.). The absence of any reference to conditions of use makes it clear that EPA must make a finding for a chemical substance as a whole, not one limited to certain conditions of use. Notably, in the final prioritization rule, EPA correctly reasoned that this type of language indicated that EPA had to consider *all* uses in prioritization. *See* 82 Fed. Reg. 33,753, 33,755 (July 20, 2017) ("The statute directs EPA to make prioritization determinations on a 'chemical substance' or 'substance,' not on 'uses,' *see, e.g.*, 15 U.S.C. §§ 2605(b)(1)(A)-(C), and in most cases, without reference to 'the conditions of use.'"). This reasoning equally applies to risk evaluations.

iii) *TSCA's purpose, as well as basic logical reasoning and the best available science, require EPA to consider all conditions of use to assess a chemical substance as a whole.*

The purpose of the risk evaluation is to analyze the risks of a substance based on an assessment of its hazards and exposures. Ignoring potential exposures at the outset undermines that purpose. And science and logic do not support EPA's exceptions. For example, EPA states that it may disregard so-called "de minimis" exposures from conditions of use that occur in a closed system or use as an intermediate (p.12). But intermediates are often not completely consumed in chemical reactions and may remain as a residual in final reaction products. *See, e.g.*, California Department of Toxic Substances Control, Spray Polyurethane Foam Systems Containing Unreacted Methylene Diphenyl Diisocyanates, http://www.dtsc.ca.gov/SCP/Spray_Polyurethane_Foam.cfm (last visited Sept. 18, 2017). So the presumption that intermediates lead to a "de minimis" exposure is often contrary to the scientific evidence. In addition, intermediates must still be manufactured as well as typically being stored, transferred, or distributed, all of which are activities that can lead to exposures – including to workers, whom TSCA expressly identifies as a "potential exposed or susceptible subpopulation." Similarly, unintended impurities or contaminants can nonetheless lead to exposures and hence risks to human health or the environment, the significance of which needs to be determined in conducting a risk evaluation. *See infra* at pp.10-11 (discussing 1,4-dioxane). Ignoring them at the outset is contrary to the purpose of TSCA and risk evaluations, as well as the law's requirement that EPA rely on the best available science.

To be sure, EDF generally agrees with EPA's statement that "all conditions of use will not warrant the same level of evaluation, and EPA expects that it may, in some cases, be able to reach conclusions without extensive or quantitative evaluations of risk." 82 Fed. Reg. at 33,734. Legally, EPA may be able to provide a concise and scientifically valid finding that a particular condition of use—such as the use phase of a chemical used as an intermediate—leads to little or no exposure and risk in a particular case, based on less than an in-depth analysis. And TSCA does not require a quantitative evaluation when a qualitative evaluation is determined and documented to be appropriate. But TSCA does not authorize EPA to simply "exclude" conditions of use at the outset as a matter of legal discretion. Furthermore, EPA must provide a scientific, data-backed rationale for why it decides a less extensive evaluation is sufficient, and cannot merely rely on a lack of data for such a decision.

EPA is imposing blinders on its analysis by asserting its authority to refuse to look at certain conditions of use, including known uses and disposals, and the result is that EPA is overlooking exposures in the real world. This approach is both contrary to law and arbitrary and capricious, as explained *infra* at Part I.D.

iv) *The legislative history does not justify or even lend support to EPA's approach.*

To justify its new position, EPA has emphasized the "legislative history" (p.11). But the legislative history, read as a whole, does not support EPA's approach. In the risk evaluation rule, EPA claims that the "legislative history of the amended TSCA *** explicitly states that the Agency is given the discretion to determine the conditions of use that the Agency will address in its evaluation." 40 Fed. Reg. at 33,728 (citing 114 Cong. Rec. S3519-20 (daily ed. June 7, 2016) (statement of Sen. Vitter)). EPA relies on a floor

statement from a single Senator, which is one of the least illuminating forms of legislative history. EPA ignores that the rest of the legislative history reveals that other Senators thought that the statutory language would require EPA to consider all conditions of use in risk evaluations under the Lautenberg Act. Four principal Democratic negotiators of the legislation submitted a statement to the record that: "[t]he definition of 'conditions of use' described above plainly covers all uses of a chemical substance." 114 Cong. Rec. S3516 (daily ed. June 7, 2016). Similarly, when explaining why the bill expressly "grandfathered" in prior risk assessments (such as for Methylene Chloride), these negotiators explained that the provision was necessary because those "risk assessments for these chemicals were not conducted across all conditions of use." *Id.* at S3519. This explanation clearly reflects that *future* risk evaluations under TSCA would have to be conducted "across all conditions of use."

Unlike the text and structure of TSCA, the legislative history is somewhat ambiguous at points, although, if anything, it supports the position that EPA must consider "all conditions of use" since more Senators expressed that view and they did so in a formal statement.

B. Conditions of use expressly include certain so-called legacy uses and associated disposals.

In each of the scopes EPA stated that it *will* exclude so-called "legacy uses" and "associated disposal," (p.12) and EPA appears to rely on its reasoning from the risk evaluation rule. 82 Fed. Reg. at 33,729-30. EPA has asserted that no statutory text addresses this issue, and EPA stated that the use of the phrase "to be" in the definition of "conditions of use" implies a prospective application. 82 Fed. Reg. at 33,730; *see* 15 U.S.C. § 2602(4) (defining conditions of use to "mean[] the circumstances *** under which a chemical substance is intended, known, or reasonably foreseen *to be* manufactured, processed, distributed in commerce, used, or disposed of") (emphasis added). EPA also (inaccurately) asserted that it did "not have an effective tool to address risks found to arise from uses in consumer settings if there" is no on-going manufacture, processing, or distribution. 82 Fed. Reg. at 33,730. But none of this reasoning survives scrutiny.

EPA's argument based on tense clearly does not apply to the legacy uses and associated disposals. If a chemical substance is present in a product or material that an industrial, commercial, or residential consumer is still using, then the substance is known "to be" used in that circumstance. Similarly, if a substance has not been disposed of yet, its disposal is in the future and reasonably foreseeable. As a result, these "legacy uses" and "associated disposal[s]" fall squarely within TSCA's definition of "conditions of use," which includes the "circumstances *** under which a chemical substance is *** known *** to be *** used, or disposed of." 15 U.S.C. § 2602(4). EPA has presented no textual basis for treating the first three participles in the list in this definition (manufactured, processed, and distributed in commerce) differently than the last two participles (used and disposed of).

EPA's theory that § 6 focuses on the "continuing flow of chemical substances" in "their lifecycles" (p.12) completely ignores that the use and disposal of a chemical is *part* of the lifecycle of a chemical, as defined by Congress in TSCA. Indeed, chemicals that are still in use are still "distributed in commerce" as that term is defined in TSCA. 15 U.S.C. § 2602(5). In the final risk evaluation rule, EPA stated that it

"believes the statute is better interpreted to focus on the prospective flow of the chemical substance," 80 Fed. Reg. at 33,730, but Congress expressly covered substances *after* their introduction into commerce as well.

EPA also justified its decision to ignore legacy uses by claiming it lacks tools to address risks from uses in consumer settings if there is no on-going commercial manufacture, processing, or distribution. 80 Fed. Reg. at 33,730. But TSCA § 6(a) expressly provides EPA with authorities that could manage some of these risks, even if it does not provide as broad authority as it does over manufacturers and processors. *See* 15 U.S.C. § 2605(a). For example, at risk management, EPA may impose "[a] requirement prohibiting or otherwise regulating any manner or method of commercial use of such substance or mixture." *Id.* § 2605(a)(5). For example, EPA could ban the sale or future use of products containing a chemical even if that chemical is no longer in production in the United States, or EPA could require that such items be labeled. EPA may also impose "[a] requirement prohibiting or otherwise regulating any manner or method of disposal of such substance or mixture, or of any article containing such substance or mixture, by its manufacturer or processor or *by any other person* who uses, or disposes of, it for commercial purposes." *Id.* § 2605(a)(6)(A) (emphasis added).

In any event, Congress expressly chose to separate risk evaluation and risk management into different procedural steps, to ensure that EPA provided a robust risk evaluation uncolored by risk management concerns. Indeed, in order to assess real-world risks of a chemical using the best available science, EPA needs to consider even those exposures over which it has limited or shared control. This approach is particularly appropriate given TSCA § 9's referral provisions.

C. The text and overall structure of TSCA makes it clear that EPA has to analyze uses, even if they have been assessed by another agency or are within another agency's jurisdiction.

EPA also stated that it may "exclude a condition of use that has been adequately assessed by another regulatory agency, particularly where the other agency has effectively managed the risk" (p.12). But EPA provides no textual basis for ignoring those uses, which are often "circumstances *** under which a chemical substance is *** known *** to be manufactured, processed, distributed in commerce, used, or disposed of." 15 U.S.C. § 2602(4). Nothing in the risk evaluation provision or definition of conditions of use authorizes EPA to ignore conditions of use because of other agencies' jurisdiction over chemical substances. And several other provisions of TSCA indicate that Congress intended for EPA to consider such exposures, except to the extent Congress explicitly provided otherwise.

First, TSCA § 9(a) provides a detailed procedural mechanism for EPA under certain circumstances to request for another federal agency to address an unreasonable risk arising from a chemical substance that EPA has identified. 15 U.S.C. § 2608(a). This request then triggers a number of duties for both EPA and the other agency, requiring one of the two agencies to take action to address the risk. Thus Congress intended for EPA to prepare risk evaluations analyzing uses that might be addressed by another agency, and Congress created a substantive and procedural mechanism to resolve overlapping jurisdiction only *after* completing the risk evaluation. If EPA could just ignore risks arising from

conditions of use that fall within other agencies' jurisdiction, or if Congress meant for EPA to defer to those agencies' current regulatory approach to those chemicals at the outset before conducting a risk evaluation, then EPA might never make the finding that triggers the § 9(a) process. Here again, Congress expressly chose to separate risk evaluation and risk management into different procedural steps, to ensure that EPA provided a robust risk evaluation uncolored by risk management concerns. Given that Congress expressly addressed the issue of overlapping regulatory jurisdictions in TSCA § 9, EPA cannot avoid those procedures by simply ignoring uses that fall within another agency's jurisdiction. Furthermore, EPA is expressly required to evaluate exposures from combinations of activities, which it cannot do if it excludes conditions of use at the outset that have been evaluated or regulated by another agency, particularly when that risk management is not an outright ban.

Second, Congress expressly exempted certain regulated chemicals or uses of chemicals from EPA's authority when it defined "chemical substance" in TSCA § 3(2). 15 U.S.C. § 2602(2)(B). For example, "chemical substance" does not include certain materials as defined in the Atomic Energy Act of 1954. *See id.* § 2602(2)(B)(ii), (iv). Thus, when Congress intended for EPA not to regulate certain conditions of use because they were regulated under other specific federal statutes, Congress expressly excluded those conditions of use. That Congress chose a limited, specific set of exclusions indicates that Congress did not intend for EPA generally to ignore other conditions of use even where they fall under other federal regulatory schemes.

D. The scopes contain incoherent and arbitrary and capricious reasoning because of EPA's approach to conditions of use.

EPA's illegal approach to "conditions of use" leads it to put "blinders" on regarding certain uses, exposures, and risks. The result is "arbitrary, capricious, [or] an abuse of discretion" under the APA, 5 U.S.C. § 706(2)(A), because it will lead EPA to have considered "factors which Congress has not intended it to consider [and] entirely failed to consider an important aspect of the problem." *State Farm*, 463 U.S. at 43. It also violates several provisions of TSCA § 26 because by ignoring uses, exposures, and related information, EPA will not be acting "consistent with the best available science," EPA will not base decisions on "on the weight of the scientific evidence," and EPA will not "take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available to the Administrator." 15 U.S.C. § 2625(h), (*i*), (k). In addition, because EPA's distinction is a false one untethered to the information, EPA seems to treat certain conditions of use inconsistently throughout the documents.

For example, in the 1,4-dioxane scope, EPA states that it will not consider risks arising from 1,4-dioxane when it is present as a by-product or residual contaminant from the manufacture of other chemicals. *See* 1,4-Dioxane, Scope at p.21, Docket ID: EPA-HQ-OPPT-2016-0723. But EPA identifies numerous products that "potentially contain[] 1,4-dioxane as a residual contaminant, including paints, coatings, lacquers, ethylene glycol-based antifreeze coolants, spray polyurethane foam, household detergents, cosmetics/toiletries, textile dyes, pharmaceuticals, foods, agricultural and veterinary products," as well as "magnetic tape and adhesives." *Id.* These are known and reasonably foreseen conditions of use

leading to exposures to 1,4-dioxane, and EPA's decision to ignore them when analyzing whether this chemical presents an unreasonable risk is arbitrary and capricious. EPA's theory is that it cannot regulate these impurities until it analyzes ethoxylated chemicals (*id.* at 8), but EPA provides no reasoned legal theory for why it could not act to regulate these exposures after this risk evaluation. *Id.* Even more problematically, EPA staked out the position that "EPA may choose not to include a particular impurity within the scope of any risk evaluation." 82 Fed. Reg. at 33,730. So these exposures may never be analyzed.

In addition, EPA acknowledges that 1,4-dioxane is often used as an intermediate or a reactant and that "the 1,4-dioxane would react either fully *or to a lesser extent*. Following completion of the reaction, the produced substance *may or may not be purified further*, thus removing unreacted 1,4-dioxane (if any exists). Reacted 1,4-dioxane is *assumed* to be destroyed and is thus not expected to be released or cause potential worker exposures." *See* 1,4-Dioxane, Scope at p.56, Docket ID: EPA-HQ-OPPT-2016-0723 (emphases added). But EPA never acknowledges that the unreacted 1,4-dioxane could lead to exposure. And that document provides no explanation, documentation, or quantification supporting the underlying assumption that 1,4-dioxane is destroyed or reacted. Indeed, from the description, it seems clear that it often will not be destroyed. The assumption in the last quoted sentence is contrary to the statements made in the proceeding sentences.

EPA's scopes should indicate that it will assess the reasonably available information on hazards and exposures for the substances (see Section II below), and that information should inform EPA's evaluation of the risks associated with "the conditions of use." If there is a real-world exposure, then EPA should not ignore it.

II. EPA must consider "reasonably available" information, and thus EPA must consider the information it already possesses and use its authorities under TSCA §§ 4 and 8 to obtain additional information.

TSCA orders EPA to consider "available" and "reasonably available" information in crafting a risk evaluation, 15 U.S.C. §§ 2605(b)(4)(F)(i), 2625(k), and under the new risk evaluation rule, EPA defined "[r]easonably available information" to mean "information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation." 40 C.F.R. § 702.33, promulgated at 82 Fed. Reg. 33,748 (July 20, 2017). Thus, under its own rule, EPA has to consider information that it "can reasonably generate, obtain, and synthesize."

Yet, the scoping documents suggest that EPA will fall far short of meeting this standard. In all of the scopes, EPA stated that it would search "readily available data and information from public sources," and "EPA encourages submission of additional existing data, such as full study reports or workplace monitoring from industry sources" (p.42). But this approach to collecting data is insufficient as a matter of law. Each scope refers to "readily available" information, but the standard under TSCA is *reasonably* available information.

A. Any information that EPA can obtain under the exercise of its authorities under §§ 8(d), 8(a), and 8(c) is "reasonably available information," so EPA must exercise those authorities.

EPA must promulgate reasonable regulations under § 8(d) and 8(a) to obtain information about hazards, exposures, and conditions of use for these ten chemicals; EPA should also exercise its authority under § 8(c) to obtain additional information. Consistent with TSCA § 8(a)(5), EPA can take steps to reduce unnecessary and duplicative reporting. Because TSCA requires EPA to produce robust risk evaluations that reflect "reasonably available" information, and information available under these authorities is "reasonably available" on its face, EPA must use these authorities to fulfill its duty. Moreover, these first ten risk evaluations are crucial to establishing the credibility of the TSCA program under the Lautenberg Act, and EPA can only establish that credibility by using its full authority to obtain "reasonably available information" on chemicals, as required by the law. Collecting this information is also necessary to fulfill EPA's duty to use the best available science under TSCA § 26.

TSCA § 8(d) allows EPA to "require any person who manufactures, processes, or distributes in commerce *** any chemical substance or mixture *** to submit to the Administrator—lists of health and safety studies: (A) conducted or initiated by or for such person with respect to such substance or mixture at any time, (B) known to such person; or (C) reasonably ascertainable by such person." 15 U.S.C. § 2607(d). EPA should issue § 8(d) rules for these ten chemicals. To obtain a complete picture, EPA should expressly require both manufacturers and processors to report on these chemicals under the § 8(d) rules. *See* 40 C.F.R. § 716.5(c).

EPA has previously issued such rules for some of these chemicals, but two decades have passed since the last of those rules sunsetted, so new, additional health and safety studies are almost certainly available. For example, the methylene chloride and asbestos reporting periods sunsetted in 1992, the HBCD reporting period sunsetted in 1995, and the perchloroethylene reporting period sunsetted in 1997. *See* 40 C.F.R. § 716.120. Given scientific advancement over the last two decades, issuing new rules calling in health and safety studies would likely provide EPA with additional valuable information to assess the hazards, exposures, and risks posed by these chemicals. It appears that EPA has never issued such rules for Carbon Tetrachloride, Trichloroethylene, Pigment Violet 29, 1-Bromopane, 1-4 Dioxane, and N-Methylpyrrolidone. *See* 40 C.F.R. § 716.120. Thus, issuing § 8(d) rules for those chemicals is even more important.

Notably, EPA's regulations correctly interpret "health and safety study" broadly to incorporate "[a]ny data that bear on the effects of a chemical substance on health or the environment." 40 C.F.R. § 716.3. These include numerous tests for health and environmental effects. *See id.* They also include monitoring data and other assessments of human and environmental exposures. *See id.* EPA should also review these studies upon receipt and request underlying data under 40 C.F.R. §§ 716.10(a)(4), 716.40(a). EPA should also separately request reporting on these chemicals when they are manufactured, processed, or distributed as an impurity, 40 C.F.R. § 716.20(a)(9), because impurities may be an important source of exposure and thus risk, as explained above.

Under TSCA § 8(a), EPA may require manufacturers and processors to provide extensive information. *See* 15 U.S.C. § 2607(a)(2). EPA "shall, to the extent feasible" "not require reporting which is unnecessary or duplicative" and also "apply any reporting obligations to those persons likely to have information relevant to the effective implementation of this title." *Id.* § 2607(a)(5). To avoid duplication, EPA need not request reporting on information EPA has already obtained through other recent submissions such as through the Chemical Data Reporting (CDR) process. *See* 40 C.F.R. Part 711. But the CDR process does not require manufacturers and processors to provide all information that EPA can reasonably obtain under TSCA § 8(a) which is relevant to the risk evaluations. For example, EPA should require reporting of: "[a]ll existing information concerning the environmental and health effects of" each chemical; "the byproducts resulting from the manufacture, processing, use, or disposal of each" chemical; more detailed information about exposures to these chemicals, including the duration, frequency, and timing of exposures; and additional information about disposal. *See* 15 U.S.C. § 2607(a)(2). In particular, EPA can require submission of any data available on releases or exposures in the workplace and environment, and those data would be crucially important to an accurate risk evaluation. To decrease the burden on industry, EPA should pursue both rulemakings simultaneously, and EPA can provide that when information is submitted under one rule, the same information need not be submitted under the other. But EPA should use both authorities to ensure that it does not miss any information that may fall within one authority but not the other.

In addition, EPA should rely on its request authority under TSCA § 8(c). Under TSCA § 8(c), "[a]ny person who manufactures, processes, or distributes in commerce any chemical substance or mixture shall maintain records of significant adverse reactions to health or the environment, as determined by the Administrator by rule, alleged to have been caused by the substance or mixture." 15 U.S.C. § 2607(c). EPA promulgated rules governing this recordkeeping requirement at 40 C.F.R. Part 717. The rules apply to most manufacturers and many processors. 40 C.F.R. § 717.5. Manufacturers and processors must maintain records of many types of allegations, as detailed in 40 C.F.R. §§ 717.5 and 717.10. The regulation defines "significant adverse reactions" to include, but not be limited to, many specific types of harm that are highly relevant to the ultimate question presented in a risk evaluation: "whether a chemical substance presents an unreasonable risk of injury to health or the environment." 15 U.S.C. § 2605(b)(4)(A). Firms must maintain these records for 30 or 5 years, depending on the circumstances. 40 C.F.R. § 717.15(d).

EPA should use its authority to request these records on alleged significant adverse reactions caused by the ten chemicals analyzed in the scope documents and add them to the administrative record for the relevant chemical. EPA can request records from manufacturers and processors that reported the chemicals in response to any § 8(a) and 8(d) rules or in response to CDR reporting. *Id.* § 717.17. EPA can request those records by letter. *Id.* § 717.17(b). Finally, EPA can also notify all people holding such records to provide them by a notice in the Federal Register. *Id.* These records may provide valuable information on hazards, exposures, and conditions of use, since the records may reveal not only significant adverse reactions but also information about the specific exposure and use that may have caused the reaction.

B. EPA must identify any information gaps and use its authority under TSCA § 4 to the fullest extent possible to fill those gaps.

EPA should make robust use of its § 4 authority to fill any gaps in information. EDF recognizes that time constraints apply to these first ten chemicals and thus some types of testing may not be possible, but going forward, EPA needs to use its authority fully and do so in a timeframe that ensures it will have all of the information it needs to conduct risk evaluations.

As EPA moves forward on the first 10 risk evaluations, it should first clearly identify *all* significant information gaps on hazards or exposures. Based on its own regulation, EPA must then use its authority under TSCA § 4(a)(2) to require the development of new information to fill those gaps wherever possible. Information that EPA can generate under TSCA § 4(a)(2) is reasonably available under EPA's own regulation as "information that EPA *** can reasonably generate [and] obtain *** for use in risk evaluations." 40 C.F.R. § 702.33. Thus, EPA should identify such information gaps and then promptly require the conduct of all testing that can be done and still meet the statutory deadlines for the risk evaluations.

TSCA § 4(a)(2) provides that EPA "may, by rule, order, or consent agreement require the development of new information relating to a chemical substance *** if the Administrator determines that the information is necessary *** to perform a risk evaluation under section 6(b)." 15 U.S.C. § 2603(a)(2)(A)(i). Congress provided this additional testing authority allowing EPA to require testing or other data development efforts solely upon a determination "that the information is necessary *** to perform a risk evaluation under section 6(b)." *Id.* In light of deadlines, EPA can and should use its order authority and does not need to make the additional findings required for a rule under TSCA § 4(a)(1).

In places in these scopes, EPA seems to be going out of its way to avoid using its information authorities. For example, in numerous places in these scopes, with respect to exposure, EPA indicates that "[f]or conditions of use where data are limited or not available, [it will] review existing exposure models that may be applicable in estimating exposure levels" (p.43). This language suggests that EPA will simply default to models rather than use its authority to get needed information. In EDF's view, EPA should first use its authorities under TSCA §§ 8 and 4 to fill those information gaps, rather than rely on models to compensate for lack of information. This is not to say that exposure models do not have a role, but they are not a basis for avoiding the obligation to collect information.

Our review of the scopes indicates that there are significant gaps in the information. Where possible EPA needs to fill those gaps. When it is not possible, consistent with TSCA § 26, EPA needs to identify those gaps and characterize the uncertainty in the draft risk evaluations. To cite just one example, in the scope for Methylene Chloride EPA completely fails to mention an information gap earlier identified in the Work Plan. Specifically, the 2014 Work Plan Assessment for Methylene Chloride identified both developmental neurotoxicity and immunotoxicity from chronic exposure as important data gaps, impacting the selection of the point of departure:

> There is uncertainty about chronic exposure impacts on the nervous system function. The nervous system has been well studied and identified as very sensitive for acute effects. However, there is a paucity of data on chronic neurological impacts, especially developmental neurotoxicity. Likewise, there is limited information about immunotoxicity following chronic exposure to DCM. Existing hazard studies are not sufficient for dose response analysis to provide a lower point of departure than existing adverse findings in the liver from chronic exposures."

See Methylene Chloride: Paint Stripping Use, TSCA Work Plan Chemical Risk Assessment at p.115, https://www.epa.gov/sites/production/files/2015-09/documents/dcm_opptworkplanra_final.pdf

C. If EPA already has relevant information, it is reasonably available and EPA should consider it.

The strategy for conducting literature searches appears to state that EPA excluded from the search "[d]ocuments not available to the public, including information stored within EPA's firewall that is not accessible on the EPA webpage (e.g., TSCA submissions) [and] Confidential Business Information." *See, e.g.*, Asbestos literature at p.13. But the information EPA has already collected about these chemicals is potentially relevant to the risks they present, even if the information is not yet publicly disclosed. This information falls squarely within EPA's definition of "reasonably available information" as "information that EPA possesses." 40 C.F.R. § 702.33. Indeed, EPA expressly stated that "[i]nformation *** is reasonably available information whether or not the information is confidential business information, that is protected from public disclosure under TSCA section 14." *Id.* Since this information is reasonably available, EPA must review it.

In addition, much of this information may not meet the new, stricter requirements and standards for nondisclosure under TSCA § 14 as amended by the Lautenberg Act. First, historically EPA has failed to review CBI claims, and while the Lautenberg Act requires EPA to do so, the public has little evidence to date that EPA is complying with this new mandate. So EPA may never have reviewed the CBI claims for this information, particularly if it was submitted before passage of the Lautenberg Act. Second, the Lautenberg Act greatly increased the requirements companies must meet to assert CBI claims. For example, information only qualifies for protection if the submitter asserts *and* substantiates that it has "a reasonable basis to believe that the information is not readily discoverable through reverse engineering." 15 U.S.C. § 2613(c). Thus, even if the information once merited protection, it may no longer be confidential under the standards of TSCA § 14. Third, as a general rule, TSCA § 14(b)(2) provides that health and safety studies and information from health and safety studies are not entitled to confidential treatment, so much of this information may not be confidential under that provision.

To fulfill its duties under TSCA, EPA must review this reasonably available information and identify that which is potentially relevant to the risk evaluations. Where information is relevant, EPA should also consider whether the information meets the strict requirements for nondisclosure under TSCA § 14. If not, EPA should add it to the administrative record for review by the public. Whether or not it meets those requirements, EPA should then determine whether and how to consider the information in evaluating these chemicals. Notably, TSCA § 26(j) requires that, "subject to section 14," EPA "shall make

available to the public *** a list of the studies considered by [EPA] in carrying out each such risk evaluation, along with the results of those studies." 15 U.S.C. § 2625(j).

D. When EPA relies on prior assessments, EPA must provide a short analysis indicating why they are sufficiently reliable to ensure that EPA is not overlooking reasonably available information.

In the literature searches, EPA sometimes states that it relied on recent assessments, and then only performed research for dates beyond those assessments. *See, e.g.*, 1,4-Dioxane, Strategy for Conducting Literature Searches for 1,4-Dioxane: Supp. File for the TSCA Scope at p.7, 9-10, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0047. EPA needs to provide a short analysis presenting its review of the prior analysis to ensure it adequately captured and addressed all reasonably available information as of the date of its publication, particularly given the expanded obligations under the Lautenberg Act. If EPA finds it was not adequate, then EPA should broaden its literature search.

III. EPA needs to take additional steps to ensure both the completeness and accuracy of the information it relies upon.

As explained above, EPA should rely on its authorities under TSCA §§ 8 and 4 to obtain all reasonably available information. Those authorities include a number of measures to ensure the accuracy and completeness of the data relied upon. To the extent EPA relies on voluntarily submitted information, EPA needs to take additional steps to ensure the accuracy and completeness of the information. Otherwise, EPA will violate TSCA § 26 by failing to make decisions "in a manner consistent with the best available science." 15 U.S.C. § 2625(h)

A. EPA has provided no sound reasoning for relying solely on voluntary requests for information, and doing so may result in limited, biased, inaccurate, or incomplete information on the chemicals.

EPA has requested in each of the scopes that industry and other stakeholders provide information. While this voluntary request was a reasonable first step towards obtaining the necessary information, EPA has failed to provide any account for how this voluntary approach to collecting information will result in EPA obtaining all "reasonably available" information as EPA has defined that term. There are several obvious problems and limitations with this voluntary approach which EPA has not even acknowledged, much less addressed.

First, a voluntary call is much less likely to produce all of the necessary information than rules mandating that affected parties provide the requested information. If manufacturers and processors are legally required to provide the information, that legal obligation provides a strong incentive for them to collect and submit all relevant information. Absent that incentive, some companies may choose to focus time and attention on other matters. Indeed, the burdens (whether one considers them heavy or light) of collecting and submitting information counsel in favor of issuing mandatory rules. *If* the process of

collecting and submitting the information is not onerous or difficult, then using rules to require the submission of the information will do little if any harm to the regulated industry, and use of rules will ensure EPA has a complete picture and increase credibility. Alternatively, to the extent that the process is onerous or difficult, it is even more important that EPA *require* the submission of the information, because otherwise those burdens will likely discourage stakeholders with relevant information from collecting and submitting the information.

Second, EPA has provided no empirical evidence establishing that this voluntary approach will result in EPA obtaining all "reasonably available" information. Unless EPA has some empirical basis for stating that the voluntary approach will allow EPA to obtain all reasonably available information that it can obtain under its legal authorities, EPA must rely on its existing authorities to obtain a complete set of information.

Indeed, EPA's prior experience with voluntary reporting provides strong evidence that a voluntary approach is unlikely to provide complete and accurate data. For example, an EPA advisory committee called for the development of nanomaterial reporting rules in 2005, but EPA instead spent several years developing and carrying out a voluntary reporting program, the Nanoscale Materials Stewardship Program (NMSP). This voluntary reporting program produced minimal information as revealed by EPA's 2009 interim report on the NMSP. Nanoscale Materials Stewardship Program, Interim Report, OPPT (Jan. 2009), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2010-0572-0003. "[I]n the report EPA estimated that companies provided information on only about 10 percent of the chemical substances manufactured at the nanoscale that may be commercially available in 2009." 80 Fed. Reg. 18,330, 18,334 (April 6, 2015). In 2017, over a decade after the data need was identified, EPA finally finalized a § 8(a) reporting rule to acquire the data. 82 Fed. Reg. 3641 (Jan. 12, 2017). Given the past failures of voluntary approaches, EPA should not rely on them here.

Third, manufacturers and processors of these chemicals have a vested interest in EPA finding that the chemicals do not present an unreasonable risk. A no-unreasonable-risk finding reduces the likelihood of government regulation, including potential restrictions on risky chemicals, and it may reduce any stigma they may otherwise face in the marketplace. The financial costs of regulation may ultimately be very high for some specific firms and individuals, and even if not, many firms and individuals may *believe* that the costs of regulation will be high. These companies have a "financial interest" in the outcome of these proceedings, and they are not impartial. *See, e.g.*, 28 U.S.C. § 455(b)(4) (requiring Judges to disqualify themselves in proceedings where they have a financial interest). Because of this reality and appearance of partiality, relying solely on voluntary measures decreases the credibility of these risk evaluations.

Relying solely on voluntary presentation of information raises the concern that the companies or trade associations may present an incomplete or skewed picture. Companies and trade associations may choose to "cherry pick" information and provide only the information that paints their chemicals in favorable light. They may provide only summaries of information that reflect conscious and subconscious judgment calls that result in unduly favorable conclusions; and without access to the full information neither EPA nor the public can independently assess such conclusions. They may choose

not to review records robustly when the review may disclose unfavorable information. They may seek to put their best foot forward and describe the ideal scenario of use and safety measures. Or, if they have unfavorable information, they may choose not to provide any information at all and simply not participate in these proceedings.

To be sure, members of the regulated community are crucial sources of information about their chemicals' uses, hazards, and exposures, but EPA cannot simply assume that they will voluntarily disclose unfavorable or complete information about their practices and products. *See* THE FEDERALIST NO. 51 (James Madison) ("If men were angels, no government would be necessary. *** [E]xperience has taught mankind the necessity of auxiliary precautions."); *Williams v. Pennsylvania*, 136 S. Ct. 1899, 1905-06 (2016) ("Bias is easy to attribute to others and difficult to discern in oneself. *** This objective risk of bias is reflected in the due process maxim that 'no man can be a judge in his own case and no man is permitted to try cases where he has an interest in the outcome.'"). Here, manufacturers and processors obviously have an interest in the outcome, and EPA must craft its procedures and approaches with that reality in mind. Requiring the submission of information is the safest approach to ensuring that these parties provide all relevant information, and that is in turn crucial to establishing and demonstrating the credibility of this process.

If EPA acts under TSCA §§ 8(a), (c), and (d), the regulations impose some requirements that will help ensure the accuracy and completeness of the information. First, EPA can require that certain information and underlying information be provided in full, which ensures completeness. In addition, a § 8(d) rule requires that people engage in an adequate search of records. 40 C.F.R. § 716.25. Second, submitters must file certification statements by authorized officials that certify that the submitted information has been submitted in compliance with the requirements of this process. *See, e.g.*, 40 C.F.R. § 711.15(b)(1). Third, submitters often must retain records of required submissions for a period of five years, and the retention of records can help encourage accurate reporting since those records would be available should a submission latter be investigated. *See, e.g.*, 40 C.F.R. § 711.25. None of these features apply to the voluntary requests for information EPA has indicated it is relying on.

In addition, as EDF has explained in prior comments, there are numerous reasons that it is important that the public have access to full studies and the underlying information, not simply robust or other study summaries. *See, e.g.*, EDF Comments on Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act, Comment at p.37, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0654-0074. Without access to full studies, the public will be challenged or unable to assess and comment on the quality of the studies used by the agency. *Id.* EDF reincorporates and reiterates the numerous points made in support of public access to the full studies here. *Id.* These points also support the importance of EPA obtaining the full studies.

B. For voluntary submissions, EPA should take additional steps to ensure completeness and accuracy and to vet information based on underlying data.

To the extent it relies on voluntary submissions, EPA can and should take additional steps to better ensure that the voluntary information it receives is accurate and complete. EPA would need to develop a far more rigorous and structured process than it currently has. For example, EPA's submission process does not appear to require anyone to certify that the information in their comments is accurate or complete to the best of their knowledge. EPA should consider approaches for vetting statements and assertions, particularly when made by entities with a financial interest in the outcome of these risk evaluations.

EPA should also request that submitters always provide full studies, as well as underlying data whenever reasonably available or obtainable. Setting aside concerns about partiality, EPA needs the underlying data to ascertain the accuracy of the information and associated statements or conclusions, as well as to determine how much confidence or uncertainty applies to a particular submission.

In addition, EPA should seek input directly from workers for manufacturers and processors, providing them an easy method to submit information on workplace practices and conditions independently from management. EPA needs to take steps to allow workers to provide input in a manner that reduces the risks of any potential retaliation from management.

To give a few specific examples from the scopes:

In the Perchloroethylene scope (also known as tetrachloroethylene or PCE), EPA cites the Vinyl Institute's comments for the fact it can be a residual or byproduct in the manufacture of other chemicals. *See* Perchloroethylene, Scope at p.24, Docket ID: EPA-HQ-OPPT-2016-0732 (citing comment at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0732-0013). That comment, in turn, contains a table claiming to summarize the approximate concentrations of Perchloroethylene in light and heavy end liquid intermediate streams yielded in the EDC/VCM process for manufacturing each of four chlorinated organic substances. The comment states that there is no residual Perchloroethylene in light liquid ends and 1.1% by typical weight in heavy liquid ends. But the comment does not provide or cite any underlying data supporting these findings. When commenters provide summary statements along these lines, EPA should give them little weight unless it also receives the underlying data to ensure that the reported results or conclusions drawn accurately reflect real-world conditions and to assess the level of certainty and scope of applicability that EPA can attribute to the results or conclusions. This point holds for all of the percentages set forth in that table, including those for the other three products.

Similar concerns arise for many of the other scopes. For example, in the Carbon Tetrachloride scope, EPA states that: "there are public comments, EPA-HQ-OPPT-2016-0733-0005 [3M] and EPA-HQ-OPPT-2016-0733-0017 [ACC], stating that carbon tetrachloride may be present in a limited number of industrial products with chlorinated ingredients at a concentration of less than 0.003% by weight." Carbon Tetrachloride, Scope at p.20, Docket ID: EPA-HQ-OPPT-2016-0733. But upon examining those

comments, they do not provide any of the underlying data or enough information to assess accuracy of the statement or the level of uncertainty that should apply to the results. The ACC comment is particularly difficult to assess. It involves multiple levels of hearsay, with ACC reporting statements that companies reported to it. Some of those companies acknowledge they are also relying on hearsay from suppliers and have not taken steps to confirm these concentrations. Those suppliers might also be relying on hearsay; it is simply not clear what the bases are for some of these values. Hearsay is, of course, particularly problematic when the statement serves the interest of the person submitting the evidence. *See, e.g.*, FED. R. EVID. P. 804(b)(5) (exception for statements against interest). As such, these concentrations arguably provide at best a "lower bound" estimate; they are not sufficient in terms of establishing that the actual concentrations are not higher. While no formal hearsay rule applies to these administrative proceedings and the hearsay evidentiary rule generally has limited applicability to technical studies and business records, it is relevant to the weight EPA should give these reported values given these circumstances. ACC does not disclose the companies providing the information, making it impossible for EPA to independently address these kinds of concerns. In addition, ACC's comment often fails to provide any clarity or detail as to how the concentrations were measured or assessed, much less provide the data underlying these claimed concentrations. The ACC comment asserts concentrations for 1,4-Dioxane, Pigment Violet 29, N-Methylpyrrolidone (NMP), Methylene Chloride (DCM), Carbon Tetrachloride, and HBCD, but for most of these concentrations, it is impossible for EPA or the public to assess whether they are accurate. For some of these concentrations, the comment states that Safety Data Sheets and Technical Data Sheets are provided with the comments, but EDF did not find any attachments with the comment containing those materials. In sum, EPA needs to scrutinize these voluntary submissions carefully and ensure access to the underlying information, which is necessary to assess the accuracy of the statements therein.

In the asbestos scoping document, EPA acknowledged that the analysis of the Chlor-Alkali industry was "primarily based on information provided by either the chlor-alkali industry or [the American Chemistry Council] and is meant to represent typical practices." *See* Asbestos, Scope at p.54, Docket ID: EPA-HQ-OPPT-2016-0736. EPA correctly recognized that EPA should "further evaluate how representative the processes witnessed at these two facilities are of processes at other plants." *Id.* at 23. EPA should take measures to ensure that its process will in fact accurately assess the full range of existing practices, relying on independent data where possible. Where independent data are unavailable, EPA should reach out to workers directly to better determine actual practices. Even when companies have good practices on paper, those practices may not be the reality on the ground.

EPA also needs to carefully scrutinize statements to ensure it correctly interprets them.

IV. These scopes are not as robust as TSCA demands, and EPA must address these flaws in the problem formulations. EPA needs to clarify what hazards, exposures, conditions of use, and susceptible populations are being considered in the risk evaluations.

Broadly viewed, the scopes do not meet several of the statutory requirements of TSCA. TSCA § 6(b)(4)(D) requires that EPA "shall, not later than 6 months after the initiation of a risk evaluation,

publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations the Administrator expects to consider." 15 U.S.C. § 2605(b)(4)(D). These scopes do not fully satisfy these requirements. Some aspects are plainly illegal under *any* interpretation of the statute, for the reasons given above, such as the statement that "EPA may determine that not all conditions of use mentioned in this scope will be included in the risk evaluation" (p.11).[1] But many other aspects, while problematic, can be resolved by EPA in the next step: its development of problem formulations.

It is often unclear in these scope documents whether EPA plans to include and evaluate in the risk evaluations the hazards, exposures, and susceptible populations it has identified. EDF believes they must be included: EPA must consider the hazards, exposures, and susceptible populations it has identified. With respect to susceptible populations, EPA should consider workers and, in most cases, pregnant women and children, to be potentially exposed or susceptible subpopulations. We identify below a number of specific examples where EPA's scopes are unclear and merit further study.

A. 1,4-Dioxane

EPA states: "EPA evaluated the weight of the evidence for cancer in humans and animals and concluded that 1,4-dioxane is 'likely to be carcinogenic to humans' based on evidence of carcinogenicity in several 2-year bioassays." 1,4-Dioxane, Scope at p.24, Docket ID: EPA-HQ-OPPT-2016-0723. However, certain language in this section suggests that EPA may not include cancer as a hazard endpoint in the risk evaluation.

Indeed, EPA almost seems to suggest that inconclusive evidence regarding the "mode of action by which 1,4-dioxane produces liver, nasal, peritoneal (mesotheliomas) and mammary gland tumors" might form a basis for disregarding the evidence of such hazards. *Id.* at 35. As a general matter, EPA should not exclude observed hazards simply because the underlying MOA is not fully delineated or understood, doing so would significantly and inappropriately jeopardize the robustness and health-protections of the risk evaluation. If there is evidence of hazard, EPA should include it in the risk evaluation, even if the precise mode of action is not yet understood.

[1] As explained above, EPA puts too much weight on a floor statement from a single Senator, David Vitter. But even Senator Vitter stated that EPA must consider all conditions of use identified in the scope. *See* 114 Cong. Rec. S3520 (daily ed. June 7, 2016) (statement of Sen. Vitter). Despite that statement, the scoping documents all state that "during problem formulation EPA may determine that not all conditions of use mentioned in this scope will be included in the risk evaluation" (p.11). Thus, EPA is inconsistent in how much weight it gives to Senator Vitter's statements, and EPA's current interpretation appears to contradict the views expressed throughout the legislative history by every single legislator. If EPA excluded uses identified in the scope, such as uses in the chlor-alkali industry (e.g., pp.20, 23-24), then EPA will be acting contrary to Senator Vitter's statement.

B. Perchloroethylene

The scope for Perchloroethylene states that "EPA expects to consider hazards identified in the recent assessment by the EPA Integrated Risk Information System (IRIS) Program: neurotoxicity, kidney toxicity, liver toxicity, developmental and reproductive toxicity and cancer. Support for an association with immune and blood effects was less well characterized." Perchloroethylene, Scope at p.11, Docket ID: EPA-HQ-OPPT-2016-0732. It is unclear from the scope whether EPA intends to include immune and blood effects in particular.

C. Trichloroethylene (TCE)

In the scope for TCE, EPA suggests that TCE's use as a spot remover will not be analyzed because it was previously analyzed in a risk evaluation. TCE, Scope at p.25, Docket ID: EPA-HQ-OPPT-2016-0737. That approach may be reasonable if EPA finalizes its proposed ban on this use of TCE to address those risks, as discussed more below. But that approach only applies to those spot remover uses that have previously been analyzed, specifically commercial dry cleaning facilities. This risk evaluation needs to consider TCE's use as a consumer spot remover. Those uses have not been analyzed in-depth, and the 2014 work plan assessment recognized that some such products may contain TCE as a main ingredient. *See* Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses, TSCA Work Plan Chemical Risk Assessment at p.52, https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf.

D. N-Methylpyrrolidone (NMP)

The NMP scope has numerous inconsistencies with respect to its identification of the endpoints to be assessed. EPA begins by acknowledging that a "number of human health hazards have been identified for NMP including adverse effects on hepatic, renal, immune, reproductive/developmental and central nervous systems." N-Methylpyrrolidone, Scope at p.36, Docket ID: EPA-HQ-OPPT-2016-0743. EPA also states that: "EPA expects to consider all potential hazards associated with NMP." *Id.* EDF completely agrees with that approach. However, the description under section 2.42 Human Health Hazards indicates that EPA intends to focus on a narrower set of hazards (acute toxicity and reproductive/developmental toxicity), and provides no justification or even explanation for excluding some of the hazards that it previously identified.

E. Potentially exposed or susceptible subpopulations

EPA also does not identify pregnant women, women of childbearing age, or the developing fetus as potential exposed or susceptible subpopulations for either N-Methylpyrrolidone (NMP) [NMP, Scope at p.35, Docket ID: EPA-HQ-OPPT-2016-0743] or TCE [TCE, Scope at pp.37-38, Docket ID: EPA-HQ-OPPT-2016-0737], despite the fact that EPA's previous risk assessments on these two chemicals identify women of childbearing age and the developing fetus as a primary susceptible population (in addition to workers). EPA's failure to identify these populations in the scopes is both contrary to law and an abuse of discretion. TSCA § 3(12) defines "potentially exposed or susceptible subpopulation" to include "a

group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance *** , such as infants, children [or] pregnant women." 15 US.C. § 2602(12). Here, EPA has previously found that "women of childbearing age" are at greater risk of adverse health effects from these chemicals. 82 Fed. Reg. 7432, 7434 (Jan. 19, 2017); 82 Fed. Reg. 7464, 7467 (Jan. 19, 2017).

Furthermore, TSCA requires that EPA identify "the potentially exposed or susceptible subpopulations the Administrator expects to consider" in the scopes. 15 US.C. § 2605(b)(4)(D). While EPA has considered those at greater risk due to *increased exposure* in the scopes to some extent, the agency appears to defer the process of identifying populations with *greater susceptibility* to the problem formulation or risk evaluation stage: "In developing the hazard assessment, EPA will also evaluate available data to ascertain whether some human receptor groups may have greater susceptibility than the general population to the chemical's hazard(s)." *See, e.g.*, NMP, Scope at pp.36-37, Docket ID: EPA-HQ-OPPT-2016-0743; 1,4-Dioxane, Scope at p.35, Docket ID: EPA-HQ-OPPT-2016-0723.

V. EPA needs to analyze potential exposures from distribution, as well as from known and reasonably foreseeable accidental exposures.

The scoping documents generally acknowledge the need to analyze activities related to a chemical's distribution, but EPA will need to analyze these exposures more robustly than the scopes currently reflect. *See, e.g.*, 1,4-Dioxane, Scope at p.22, Docket ID: Docket ID: EPA-HQ-OPPT-2016-0723.

The scoping documents give little, if any, attention to potential releases and exposures resulting from accidental releases. EDF does not suggest that EPA needs to consider every possible scenario, but the risk of accidental releases and exposures is very real and certainly "reasonably foreseen" in many respects, and EPA has authority to mandate steps to reduce those risks. For example, as and after Hurricane Harvey passed through Houston, over 40 sites released toxic chemicals into the environment. *See, e.g.*, More Than 40 Sites Released Hazardous Pollutants Because of Hurricane Harvey, https://www.nytimes.com/interactive/2017/09/08/us/houston-hurricane-harvey-harzardous-chemicals.html?_r=0. Given the *known* accidental releases, the huge number of petrochemical plants and refineries in the Houston area, and the likelihood that flooding there may become more common in light of climate change, such events are clearly reasonably foreseen and hence EPA needs to give more consideration to the potential for accidental releases.

VI. EPA should not rely on labeling and PPE as a basis to assume low or no exposure, given the major real-world limitations of these measures.

Language used in the scopes suggests that EPA may inaccurately assume that people comply with all warning labels and always use personal protective equipment (PPE). EDF strongly urges EPA to consider real-world exposures reflecting the reality of the sometimes low-compliance with or non-existence of these measures. EPA should account for such real-world limitations of PPE in the risk evaluations by

either collecting or requiring the development of empirical data, or, in their absence, using worst-case assumptions to assess the extent of exposure reduction resulting from labeling and PPE. Reliance on such data clearly constitutes best available science (a requirement under TSCA § 26), and EPA has clear authority to collect or require the development of such data under § 4(b)(2)(A). And absent empirical evidence establishing the extent to which people are using these measures, EPA should assume that they may not be. Indeed, EPA's need for accurate information about actual compliance is another reason to rely on its authorities under TSCA § 8 to mandate that manufacturers and processors provide that information. In addition, it bears noting that reliance on PPE as a primary measure to protect workers is counter to OSHA's Industrial Hygiene Hierarchy of Controls (HOC), a long-standing principle that prioritizes measures to eliminate or reduce the presence of a hazard in occupational settings (e.g., substitution/use of less toxic chemicals and institution of engineering controls) over measures that shift burdens onto the workers themselves, such as through reliance on PPE and warning labels. The HOC exemplifies the best available science for creating safe, healthful workplace environments.

As an example of a problematic reference to PPE in the scopes, in the asbestos scope, EPA stated that "[d]ermal exposure is unlikely due to glove use in the workplace." Asbestos, Scope at p.37, Docket ID: EPA-HQ-OPPT-2016-0736. But EPA cites no evidence supporting this assumption. While gloves may be used in many workplaces, EPA needs to provide evidence of the extent of such use. Among other things, EPA correctly noted earlier that "certain conditions of use, such as a mechanic changing asbestos-containing brakes, may also result in dermal exposure." *Id.* at 35. Is there any evidence that all or even most mechanics wear gloves when changing brakes? Indeed, EPA should identify mechanics as a relevant potentially exposed or susceptible subpopulation based on their exposure to brakes.

In comments EDF has submitted in these dockets, EDF previously commented on the serious limitations of labeling and PPE, as well as the importance of adherence to the hierarchy of controls to limit workplace exposures. *See, e.g.*, EDF comments at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0046, March 15, 2017; and at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2014-0650-0052, November 21, 2016. EDF reincorporates and reiterates the points made in those comments here.

VII. EPA's decision not to examine uses addressed by its planned § 6(a) rules governing certain uses of TCE, DCM, and NMP is only justified if EPA plans to move forward with risk management rules that ban these uses and thereby eliminate the unreasonable risks previously identified for these uses.

For Trichloroethylene (TCE), Methylene Chloride (DCM), and N-Methylpyrrolidone (NMP), EPA states that conditions of use previously examined will not be re-evaluated. TCE, Scope at p.9, Docket ID: EPA-HQ-OPPT-2016-0737; DCM, Scope at p.29, Docket ID: EPA-HQ-OPPT-2016-0742 ("This includes uses assessed in the U.S. EPA (2014a) risk assessment and therefore those uses are out of scope for the risk evaluation."); NMP, Scope at pp.20, 28, Docket ID: EPA-HQ-OPPT-2016-0743 ("This includes uses assessed in the previous EPA risk assessment (U.S. EPA, 2015) and therefore those uses are out of scope for the risk evaluation."). EPA has previously found these uses even by themselves present unreasonable risks to human health. In addition, these uses have the potential to increase the total

exposure of people to these chemicals. As a result, EPA can only reasonably exclude these uses if it finalizes the proposed rules to ban these uses. EDF strongly supports those bans for the reasons it articulated in its prior comments.

If EPA does not finalize these bans, then excluding these uses is both contrary to law and arbitrary and capricious. By definition, EPA has already found these uses to be "conditions of use" as "the circumstances, as determined by the Administrator, under which a chemical substance is *** known *** to be manufactured, processed, distributed in commerce, used, or disposed of." 15 U.S.C. § 2605(b)(4)(A), 2602(4). In addition, EPA has already found that these uses present unreasonable risks. It would be absurd for EPA to exclude these uses *unless* EPA has already banned these uses to eliminate the unreasonable risks and ensure that such uses no longer present any residual risk which would otherwise need to be included in the present risk evaluations for those chemicals.

* * * * *

EDF appreciates the opportunity to provide comments and EPA's consideration of them.

charles river

DRAFT PROTOCOL

Testing Facility Study No. 00459506

An Oral (Drinking Water) Study of the Effects of Trichloroethylene (TCE) on Fetal Heart Development in Sprague Dawley Rats

SPONSOR:
Halogenated Solvents Industry Alliance, Inc.
3033 Wilson Boulevard, Suite 700
Arlington, VA 22201
USA

TESTING FACILITY:
Charles River Laboratories Ashland, LLC
1407 George Road
Ashland, OH 44805
United States

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1. OBJECTIVES

The objective of this study is to determine the potential of trichloroethylene (TCE) to induce cardiac defects in the offspring after maternal exposure from the day after copulation to 1 day prior to expected parturition, to characterize maternal toxicity at the exposure levels tested and to determine a NOAEL (no-observed-adverse-effect level) for maternal and cardiac developmental toxicity.

In addition, plasma concentrations of ~~TCE and~~ TCA (trichloroacetic acid, the primary metabolite of trichloroethylene) will be assessed in maternal and fetal plasma.

Commented [PSC1]: Removed verbiage pertaining to TCE concentration assessment

1.1. Study Classification

Study Category:	Developmental and Reproductive Toxicology
Study Type:	Prenatal Development
Study Design:	Parallel
Primary Treatment CAS Registry Number:	79-01-6
Primary Treatment Unique Ingredient ID:	Trichloroethylene
Class of Compound:	Solvent

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Animal Arrival:	~~To be determined~~17 Jul 2018
Initiation of Dosing:	~~To be determined~~25 Jul 2018
Completion of In-life:	~~To be determined~~20 Aug 2018
Audited Draft Report:	~~To be determined~~29 Oct 2018

3. GUIDELINES FOR STUDY DESIGN

This study will be conducted in general accordance with the United States Environmental Protection Agency (EPA) Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August 1998, and the Organisation of Economic Cooperation and Development Guidelines (OECD) for the Testing of Chemicals Guideline 414, Prenatal Developmental Toxicity Study, January 2001.

4. REGULATORY COMPLIANCE

This study will be conducted in compliance with the United States Environmental Protection Agency (EPA) TSCA (40 CFR Part 792) Good Laboratory Practice Standards and as accepted by regulatory authorities throughout the European Union (Organization for Economic Cooperation and Development), Japan, and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement. Exceptions to GLPs include the following study elements:

- Test substance characterization will not be conducted according to GLP standards.
- ~~Assessment of concentrations of TCE in maternal and fetal plasma will not be conducted according to GLP standards. A qualified laboratory method developed at Charles River Ashland will be used.~~

Commented [PSC2]: Removed verbiage pertaining to TCE concentration assessment

5. QUALITY ASSURANCE

5.1. Testing Facility

The Testing Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the protocol, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Testing Facility QAU contact for this study is indicated below:

Heather L. Johnson, BS, RQAP-GLP
Charles River
1407 George Road
Ashland, OH 44805
Tel: 419.289.8700 x 6874
Fax: 419.289.3650
E-mail: heather.johnson@crl.com

6. SPONSOR

Sponsor Representative

Christopher J. Bevan, PhD, DABT
Director, Scientific Programs
Halogenated Solvents Industry Alliance, Inc.
Address as cited for Sponsor.
Tel: (703) 875-0684
Cell: (513) 646-1468
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Sponsor Study Monitor

Raymond G York, PhD, DABT, ATS, ERT
RG York & Associates LLC
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Cincinnati, OH 45245
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Email: ryork2@outlook.com

7. RESPONSIBLE PERSONNEL

Study Director

Prägati Sawhney Coder, PhD, DABT
Director, Developmental and Reproductive Toxicology
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Email: pragati.coder@crl.com

Alternate Contact

Mark T. Herberth, PS, LATG
Senior Research Scientist, Developmental and Reproductive Toxicology
Address as cited for Testing Facility
Tel: (419) 289-8700
Email: mark.herberth@crl.com

Commented [PSC3]: Added Mark as an alternate contact. Mark is a Senior Research Scientist in my group and will serve as backup for technical questions from the staff, in the event that I am unavailable.

Management Contact

Donald G. Stump, PhD, DABT
Senior Director, Toxicology
Address as cited for Testing Facility
Tel: (419) 289-8700
Fax: (419) 287-3650
Email: donald.Stump@crl.com

Individual Scientists (IS) at the Testing Facility

Dose Formulation Analysis	Shiladitya Sen, PhD Senior Research Scientist, Analytical Chemistry Address as cited for Testing Facility Tel: (419) 289-8700 Fax: (419) 287-3650 Email: Shiladitya.Sen@crl.com

Plasma Analysis	Joelle Lucarell, PhD Research Scientist II, Bioanalytical Chemistry Address as cited for Testing Facility Tel: (419) 289-8700 Fax: (419) 287-3650 Email: Joelle.Lucarell@crl.com

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner and the Study Director will provide notification to the Sponsor Representative within 24 hours. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase.

8. TEST SUBSTANCE, POSITIVE CONTROL SUBSTANCE AND VEHICLE DATA

8.1. Test Substance

8.1.1. Identification

Trichloroethylene (TCE) (CAS No. 79-01-6) ≥99% and scavenger-free

Purchased from Spectrum Chemical Manufacturing Corp. (T1115 reagent grade, or equivalent).

8.1.2. Characterization

Lot numbers, purity, stability, and storage conditions will be provided by the Supplier/Manufacturer, documented in the study records and included in the Final Report.

8.1.3. Storage Conditions

In a room with controls set to maintain 18°C to 24°C, protected from light.

8.1.4. Physical Description

To be documented by Charles River.

8.1.5. Reserve Samples

Commented [PSC4]: Minor edits per current CRL protocol template

Reserve samples of the test substance will be taken in accordance with Charles River Standard Operating Procedures and stored in the Charles River Archives ~~indefinitely unless otherwise specified~~.

8.1.6. Personnel Safety Data

A ~~Material~~ Safety Data Sheet (MSDS) is to be provided by the Supplier/Manufacturer. Standard safety precautions will apply.

8.1.7. Test Article Disposition

With the exception of the reserve sample for each batch of test article (if applicable), all neat test article remaining at study completion will be discarded appropriately.

8.2. Positive Control Substance

8.2.1. Identification

all-*trans* Retinoic Acid ≥98% by HPLC (CAS No. 302-79-4)

Purchased from Sigma-Aldrich, Inc. (R2625, or equivalent)

8.2.2. Characterization

Lot numbers, purity, stability, and storage conditions will be provided by the Supplier/Manufacturer, documented in the study records and included in the Final Report.

8.2.3. Storage Conditions

In a freezer, set to maintain -20°C, protected from light.

8.2.4. Physical Description

To be documented by Charles River

8.2.5. Reserve Samples

Commented [PSC5]: Minor edits per current CRL protocol template.

Reserve samples of the positive control substance will be taken in accordance with Charles River Standard Operating Procedures and stored in the Charles River Archives ~~indefinitely unless otherwise specified~~.

8.2.6. Personal Safety Data

A ~~Material~~ Safety Data Sheet (~~M~~SDS) is to be provided by the Supplier/Manufacturer. Standard safety precautions will apply.

8.3. Vehicle (for Drinking Water Formulations)

8.3.1. Identification

Reverse osmosis-purified water

8.3.2. Characterization

Water used on-site is subject to routine monitoring as indicated in SOP A-067. Standard safety precautions will apply.

8.4. Vehicle (for Positive Control Formulations)

8.4.1. Identification

Soybean oil (CAS No. 8001-22-7)

Purchased from Sigma-Aldrich, Inc. (S7381 dietary grade, or equivalent)

8.4.2. Characterization

Lot numbers, purity, stability, and storage conditions will be provided by the Supplier/Manufacturer, documented in the study records and included in the Final Report.

9. PREPARATION AND ANALYSIS OF TEST AND POSITIVE CONTROL SUBSTANCE FORMULATIONS

9.1. Test Substance Formulations

Commented [PSC6]: Section updated per changes successfully incorporated during the Feasibility study 00459507

9.1.1. Method and Frequency of Preparation

Based on the physical characteristics of the test substance, appropriate methods will be used to ensure the best possible formulations of the test substance in the vehicle. Test substance formulations will be prepared daily, in a closed system, under amber light, without sonication, and stored and transported in the same closed system amber formulation bottles (for light protection). Each amber formulation bottle will be purged with nitrogen, sealed with a foil liner and silicone septum fitted with a fabricated siphon valve system built at Charles River Ashland.

All formulation batches will be prepared at volumes large enough to minimize headspace. The 500 and 1000 ppm concentrations will be prepared the day prior to dosing and stirred overnight at room temperature for at least 24 hours. The 0.25 and 1.5 ppm concentrations will be prepared via dilution of higher concentrations on the day of dose administration. Test substance formulations will be stored at room temperature (18°C to 24°C) following preparation and until transfer into drinking water bottles for administration to study animals.

For transfer into drinking water bottles, the inlet valve on each formulation bottle will be connected to a nitrogen source to allow nitrogen to displace dosing formulations that are removed via the outlet valve. Purging of any headspace with nitrogen will help reduce volatilization of TCE and ensures that residual water formulations do not come in contact with ambient air. Drinking water bottles will be filled by allowing the water to flow along the inner wall, to reduce splashing, bubbling and volatilization of TCE.

~~Special precautions will be taken to ensure that dosing formulations are prepared and transported in a closed system, and all closed formulation containers will be purged with nitrogen. All formulations will be prepared at volumes that minimize headspace in the preparation vessels. All dose concentrations at or above 100 ppm will be prepared the day prior to dosing and stirred overnight at room temperature for at least 24 hours. Concentrations below 100 ppm will be prepared via dilution of higher concentrations on the day of dose administration. Test substance~~

formulations will be stored at room temperature (18°C to 24°C) following preparation and until transfer into drinking water bottles for administration to study animals. Test substance formulations will be transferred into drinking water bottles via a sealed valve system built at Charles River Ashland.

Any procedures not covered by SOPs required for formulation will be approved by the Study Director and included in the study records.

The Study Director or designee will visually inspect the test substance formulations prior to initiation of dosing. This visual inspection will be performed to ensure that the formulations are visibly homogeneous and acceptable for dosing.

9.1.2. Solubility and Stability of Test Substance in Drinking Water Formulations

Test substance formulations in drinking water will be analyzed using a method previously developed and validated at Charles River Ashland.[1] Solubility and stability of the test substance in the vehicle following room temperature (18°C to 24°C) storage for at least 24 hours, and following frozen (purged with nitrogen, -10°C to -20°C) storage, at the range of concentrations being used on the current study was previously established.[NOTEREF _Ref504930085 \h * MERGEFORMAT] Therefore, solubility and stability and homogeneity/solubility of test substance formulations will not be assessed on the current study.

9.1.3. Concentration of Test Substance in Drinking Water Formulations

Concentration of test substance in "as-delivered" dosing formulations, including the vehicle control, will be assessed on the 1st, 2nd, 3rd, 7th, 12th, 15th, 22nd and last batch of drinking water formulations. For analytical purposes, the last batch will be the last day all prepared batches (at all concentrations) are used for administration to animals (i.e. taking into consideration breeding stagger). Samples for possible concentration assessment will also be collected from all remaining daily batches, purged with nitrogen, and stored in a freezer set to maintain a target of -20°C.

Sampling, processing and analysis of prepared drinking water formulations will be conducted on the day of distribution prior to transfer into drinking water bottles for administration to study animals according to the table below. For preparations scheduled for analysis, samples will be processed and analyzed as soon as possible following collection.

Test Substance Formulation Sampling Scheme

Group(s)	Time of Sampling	Formulation Container	Sample Scheme and Volume[a]	Formulation Preparation Number(s)[b]
1, 3-6	Time of Prep (Closed System)	Amber Formulation Bottle	2 x 10 mL	First, 2nd, 3rd, 7th, 12th, 15th, 22nd and Last
1, 3-6	Time of Dispensation (Open System)	Amber Drinking Water Bottle	2 x 10 mL	First, 2nd, 3rd, 7th, 12th, 15th, 22nd and Last
1, 3-6	24h Post-Dispensation (Open System)	Amber Drinking Water Bottle	(2 x 10 mL) x 3 bottles	First, 2nd, 3rd, 7th, 12th, 15th, 22nd and Last

[a] All samples will be collected from the middle stratum, into amber glass auto-sampler vials with rubber

stoppers, and crimped tops.

[b] For analytical purposes, the last batch will be the last day all prepared batches (at all concentrations) are used for administration to animals (i.e. taking into consideration breeding stagger).

All samples will be collected in amber glass auto-sampler vials with rubber stoppers and crimped tops. Following acceptance of each set of analytical results, by the study director and the Sponsor Representative, any prior unanalyzed batches up until that point will be discarded appropriately (e.g. following analysis of the 7th batch, and acceptance of the analytical results, samples from the 4th, 5th and 6th (unanalyzed) batches will be discarded.

) For analytical purposes, the last batch will be the last day all prepared batches (at all concentrations) are used for administration to animals (i.e. taking into consideration breeding stagger). Sampling, processing and analysis of prepared drinking water formulations will be conducted on the day of distribution prior to transfer into drinking water bottles for administration to study animals. Two 1.0 mL samples will be collected from the middle of the vehicle control and each test substance drinking water formulation for assessment of the concentration of the test substance in the formulations. Samples will be processed and analyzed as soon as possible following collection.

No additional sampling or analysis of drinking water formulations will be conducted following transfer to an open system (i.e. drinking water bottles) with the exception of 24-Hour loss monitoring as described below. For consistency and ease of reporting, concentrations for each dose group in the protocol and report tables will be referred to by the initial (target) concentration as has been used in previously published reports.[2,3] Calculated compound consumption will be based on analytically confirmed concentrations at each assessment interval. The target acceptance criteria for concentration assessment of TCE in drinking water formulations will be mean concentrations within 100% ± 20% (80-120%) of the target concentration. However, because of the volatility of the test substance, it is recognized that this acceptance criteria may not be achievable for each formulation and concentration. If any formulations do not met acceptance criteria, the impact of the out-of-specification results will be addressed in the report.

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24-hour Loss Monitoring – Samples collected 24-hours post-dispensation will be collected from "used" water bottles in the animal room and will be processed and analyzed for concentration assessment as soon as possible following collection. Because of the open system and the volatility of the test substance, measured concentrations will be reported as-is i.e. target acceptance criteria will not apply to 24-hour loss monitoring samples. Loss of TCE at each concentration, will be calculated by averaging of the three sampled bottles and comparison against corresponding Time Zero concentrations (measured concentrations prior to transfer into drinking water bottles) and will be reported as a Percent 24-Hour Loss for each concentration.

In order to determine how much TCE is lost from drinking water formulations over the course of 24-hours in an open system (i.e. drinking water bottles), formulations from the first batch will be sampled following approximately 24-hours of administration to animals. Two 1.0 mL samples will be collected from the middle of the vehicle control, and from 3 randomly selected bottles with test substance drinking water formulation (at each concentration). Samples will be taken

from "used" water bottles in the animal room and will be processed and analyzed for concentration assessment as soon as possible following collection. Because of the open system and the volatility of the test substance, measured concentrations will be reported as-is i.e. target acceptance criteria will not apply to 24-hour loss monitoring samples. Loss of TCE at each concentration, will be calculated by averaging of the three sampled bottles and comparison against corresponding Time Zero concentrations (measured concentrations prior to transfer into drinking water bottles) and will be reported as a Percent 24-Hour Loss for each concentration.

The final analytical report will be incorporated as an appendix to the Charles River final report.

9.2. Positive Control Substance

9.2.1. Method and Frequency of Preparation

Based on the physical characteristics of the positive control substance, appropriate methods will be used to ensure the best possible formulations in the vehicle, soybean oil, which may be warmed to ensure solubilization, if necessary. Positive control substance formulations will be prepared under amber light and stored and transported in small amber aliquot bottles for light protection. Positive control substance formulations will normally be prepared approximately weekly, divided into aliquots for daily dispensation, purged with nitrogen and stored in a freezer, set to maintain a target of -20°C. The positive control formulations will be thawed for each day of administration, and dispensed after remixing for a minimum of 30 minutes using a magnetic stirrer. Positive control formulations will be stirred continuously during dosing.

Any procedures not covered by SOPs required for formulation will be added to the protocol by protocol amendment and presented in the final report of this study.

9.2.2. Concentration of Positive Control Substance in Soybean Oil Formulations

Positive control formulations in the vehicle, soybean oil, will not be assessed for solubility, concentration, homogeneity, or stability. All-*trans* retinoic acid (RA) is a commercially available drug substance that will be prepared according to package specifications. It is a well characterized developmental toxicant that has been previously demonstrated to result in heart malformations in this strain of rat.[4]

Sampling of positive control substance dosing formulations will be conducted for For future possible concentration assessments will be conducted according to the table below. of Samples will be purged with nitrogen and concentration of the positive control substance in dosing formulations, duplicate 1.0 mL samples will be collected from the middle strata on the first and last day of use for each batch of dosing formulations. Samples will be purged with nitrogen and stored in a freezer set to maintain a target of -20°C.

Positive Control Substance Formulation Sampling Scheme

Group(s)	Time of Sampling	Formulation Container	Sample Scheme and Volume	Formulation Preparation Number(s)
2	Time of Prep	First Aliquot	2 x 1 mL	All

2	Time of Dispensation	Last Aliquot	2 x 1 mL	All

If samples are analyzed, the final analytical report will be incorporated as an appendix to the Charles River final report.

Following completion of the in-life phase of the study and the acceptance of study results by the study director and the Sponsor Representative, any unanalyzed samples will be discarded appropriately (i.e. samples will not be archived, but will be discarded prior to issuance of the final report).

10. TEST SYSTEM

Species:	Rat
Strain:	Sprague Dawley Crl:CD(SD)
Condition:	Naïve, Nonpregnant
Source:	Charles River Laboratories, Inc. (Raleigh, North Carolina)
Number of Males Ordered:	A sufficient number of sexually mature untreated resident males of the same strain and source will be purchased to induce pregnancies.
Number of Females Ordered:	210
Target Age at the Initiation of Breeding:	80 to 120 days at the initiation of breeding
Target Weight on Gestation Day 0:	A minimum of 220 g

Animals not assigned to the study will be transferred to the animal colony or will be euthanized by carbon dioxide inhalation and the carcasses discarded. The actual age and weight of animals received will be listed in the Final Report.

10.1. Identification System

A permanent animal number will be assigned to each individual animal. Each animal will be identified using a subcutaneously implanted electronic identification microchip (BMDS system). The microchip will be the primary means to uniquely identify animals assigned to study. Individual cage cards will be affixed to each cage and will display at least the animal number, group number, dosage level, study number, and sex of the animal.

Replacement microchips may be implanted as necessary throughout the course of the study. An ear tag may be used as the alternate unique identifier.

10.2. Justification for Selection

The purpose of this study is to replicate the findings of Dawson et al.[NOTEREF _Ref511308716 \h * MERGEFORMAT] and Johnson et al.[NOTEREF _Ref504935597 \h * MERGEFORMAT] In these studies it was

reported that there was an increase in cardiac malformations in the fetuses of pregnant female Sprague Dawley rats administered TCE in drinking water.

This species and strain of rat has been recognized as appropriate for developmental toxicity studies. Charles River has historical data on the background incidence of fetal malformations and developmental variations in this species from the same strain and source. This animal model has been proven to be susceptible to the effects of developmental toxicants

10.3. Number of Study Animals

The number of animals is based on the US EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Development Toxicity Study, August 1998 and the OECD Guidelines for the Testing of Chemicals: Guideline 414, Prenatal Developmental Toxicity Study, January 2001, which recommend evaluation of approximately 20 females with implantation sites at necropsy. Given the possibility of nongravid animals, unexpected deaths, or treatment-related moribundity and/or mortality, 25 females/group is an appropriate number to obtain a sample size of 20 females at termination.

The number of animals assigned to the toxicokinetic phase (4 females/group) is also based on the possibility of nongravid animals, unexpected deaths, or treatment-related moribundity and/or mortality; this is an appropriate number of animals to obtain at least 3 blood samples per time point.

11. SPECIFIC ANIMAL MAINTENANCE SCHEDULE

11.1. Animal Receipt and Acclimation

Each rat will be inspected by a qualified technician upon receipt. Rats judged to be in good health and suitable as test animals will be immediately placed in acclimation for a minimum of 7 days. All rats will be initially weighed, permanently identified with a microchip, and will receive a detailed clinical observation. During the acclimation period, each rat will be observed twice daily for changes in general appearance and behavior. Body weights will be recorded prior to the initiation of breeding. Prior to the start of breeding, those rats judged to be suitable test subjects will be identified.

During social housing, some observations (e.g., fecal observations) may not be attributable to an individual animal. In these instances, observations will be recorded in a separate computer file for the social group.

11.2. Animal Housing

Female rats will be housed, 2-3 per cage, in clean solid-bottom cages with bedding material (Bed O'Cobs® or other suitable material) for at least 3 days following receipt in an environmentally controlled room. Following positive signs of mating, each female will be individually housed in clean, solid-bottom cages with bedding material (Bed O'Cobs® or other suitable material) until euthanasia. Animals may be temporarily separated for protocol-specified

activities and this will be documented in the study records. In addition, animals may be individually housed due to incompatible behavior with a cage mate(s) or for health monitoring purposes requested by the veterinarian. Animals whose cage mate(s) are removed from study (morbidity, unscheduled death, etc.) will not be re-paired but will remain individually housed for the remainder of the study.

The cages will be subjected to routine cleaning at a frequency consistent with maintaining good animal health and Charles River Standard Operating Procedures. The facilities at Charles River Ashland are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

Individual housing of presumed pregnant females is required to adequately monitor the health of these females by allowing collection of individual food consumption and appropriate identification of cage observations in the event of abortion or early delivery

11.3. Environmental Conditions

Controls will be set to maintain temperature at 73 ± 5°F (23 ± 3°C) and relative humidity at 50 ± 20%. Temperature and relative humidity will be monitored continuously. Data for these 2 parameters will be scheduled for automatic collection on an hourly basis. Fluorescent lighting controlled by light timers will provide illumination for a 12-hour light/dark photoperiod. The ventilation rate will be set at a minimum of 10 room air changes per hour, 100% fresh air.

11.4. Drinking Water

Cage banks will not be connected to the automated watering system. Reverse osmosis-purified water (with test substance added during the treatment period for animals assigned to Groups 3-6) will be available *ad libitum* via amber glass water bottles with metal sipper tubes. Bottles will be checked daily for spillage and supplemented as necessary and the occurrence of spillage will be documented. During the treatment period, bottles will be changed daily. The municipal water supplying the laboratory is analyzed according to Charles River Ashland SOPs on a routine basis to ensure that contaminants are not present in concentrations that would be expected to affect the outcome of the study.

11.5. Basal Diet

PMI Nutrition International, LLC Certified Rodent LabDiet® 5002 will be offered *ad libitum* during the study. Periodic analyses of the certified feed are performed by the manufacturer to ensure that heavy metals and pesticides are not present at concentrations that would be expected to affect the outcome of the study. Results of the analyses are provided to Charles River by the manufacturer. Feeders will be changed and sanitized once per week.

11.6. Environmental Enrichment

Enrichment devices will be provided to each animal for environmental enrichment beginning during acclimation, and continuing throughout the course of the study.

12. EXPERIMENTAL DESIGN

12.1. Breeding Procedure

At the conclusion of the acclimation period, female rats judged to be suitable test subjects and meeting acceptable body weight requirements will be cohabitated with untreated resident male rats (1:1) of the same strain and source in solid-bottom cages for mating. Detection of mating will be confirmed by the appearance of a vaginal copulatory plug or by evidence of sperm in a vaginal lavage. Vaginal lavages will be performed daily during the mating period until evidence of mating is observed. After confirmation of mating, the female will be returned to an individual solid bottom cage (assigned to a group), and the day will be designated as day 0 of gestation.

12.2. Animal Selection and Randomization

Mated females will be assigned to groups using a WIL Toxicology Data Management System (WTDMS™) computer program which assigns animals based on stratification of Gestation Day 0 body weights into a block design to 1 vehicle control group, 1 positive control group and 4 test substance groups of 25 rats each for the prenatal developmental (Main) phase. For the exposure assessment (Exp.) phase, the vehicle control and 4 test substance groups will consist of 4 rats each.

Following the initiation of dosing, it may be necessary to add individual animal(s) (due to animals being found dead, euthanized *in extremis*, exhibiting abnormal clinical signs, reduced food consumption, body weigh losses, or dosing errors). Individual animals that are added to the study will be selected from the remaining unassigned mated animals, and assigned arbitrarily (not computer randomized) to the study based on comparable body weights (if possible) with respect to the animal(s) previously assigned to the study. The reason(s) for adding the animal(s) will be appropriately documented in the study records. The cut-off gestation age for adding animals to study is Gestation Day 1 for the vehicle control and test substance groups and Gestation Day 6 for the positive control group.

12.3. Organization of Test Groups, Dosage Levels, and Treatment Regimen

12.3.1. Rationale for Dose Selection

The dosage levels were selected based on previous published reports assessing fetal heart development in Sprague Dawley rats[NOTEREF _Ref504935597 \h],[NOTEREF _Ref461106285 \h * MERGEFORMAT],5 and were provided by the Sponsor Representative after consultation with the Charles River Study Director.

The positive control substance, RA, is a well characterized developmental toxicant that has been previously demonstrated to result in heart malformations in this strain of rat. The dosage level of RA was also selected based on previously published reports.[NOTEREF _Ref461106285 \h * MERGEFORMAT]

12.3.2. Organization of Test Groups

The following table presents the study group arrangement.

Study Design

Group Number	Test Substance	Dosage Level (mg/kg/day)	Dose Concentration	Dose Volume (mL/kg)	Route of Administration	Number of Females	
						Main	Exp.
1	Vehicle control	0	0 ppm	NA	Drinking Water	25	4
2	RA	15	3 mg/mL	5	Gavage	25	0
3	TCE	a	0.25 ppm	NA	Drinking Water	25	4
4	TCE	a	1.5 ppm	NA	Drinking Water	25	4
5	TCE	a	500 ppm	NA	Drinking Water	25	4
6	TCE	a	1000 ppm	NA	Drinking Water	25	4

a Dosage levels for the drinking water groups (i.e. mean amount of TCE received by each group of rats) will be calculated upon completion of the study based on mean water consumption of each group and target concentration of the test substance in water formulations. For consistency and ease of reporting, concentrations for each dose group will be referred to by the initial target concentration as has been used in previously published reports.[NOTEREF _Ref304935597 \h * MERGEFORMAT]

12.3.3. Route and Rationale of Test Article Administration

The route of administration of the test substance will be oral (drinking water) as this is a potential route of exposure for humans.

The positive control substance, RA, will be administered via oral (gavage) as that route of exposure has been demonstrated to elicit a positive response.[NOTEREF _Ref461106285 \h * MERGEFORMAT]

12.3.4. Treatment Regimen - Test and Positive Control Substances

Vehicle control or test substance drinking water formulations will be offered *ad libitum* from Gestation Day 1 through euthanasia (scheduled for Gestation Day 21). Water formulations will be supplied fresh on a daily basis, within ± 2-3 hours from the previous day.

The positive control substance will be administered as a single daily dose from Gestation Day 6 through 15, inclusively (Group 2 only). This is the standard dosing regimen for a prenatal developmental toxicity study and is expected to elicit a positive response.[NOTEREF _Ref461106285 \h * MERGEFORMAT] All rats will be dosed at approximately the same time each day.

The positive control group (Group 2) will receive vehicle control drinking water formulations *ad libitum* from Gestation Day 1 through euthanasia. Water formulations will be supplied fresh on a daily basis.

12.3.5. Method of Test Article Administration

Control and treated drinking water formulations will be offered *ad libitum* in amber glass water bottles with metal sipper tubes. Water bottles will be changed and sanitized daily, and drinking water formulations will be supplied fresh on a daily basis.

The positive control substance will be administered orally by gavage (Group 2 only) using appropriately sized disposable plastic feeding tubes (Instech Laboratories, Plymouth Meeting, PA). The dose volume will be 5 mL/kg. Formulations will be stirred continuously at room temperature for the duration of the dosing procedure.

12.3.6. Adjustment of Dose Volumes

The test substance will be administered as a constant concentration (ppm) in water.

For the positive control substance treated group (Group 2), individual dosages will be calculated on the most recent body weight to provide the proper mg/kg/day dosage.

13. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

13.1. Viability Observations

Each rat will be observed twice daily for moribundity and mortality, once in the morning and once in the afternoon from Gestation Day 0 until euthanasia.

13.2. Maternal Observations during Gestation

Detailed clinical observations will be recorded daily prior to administration of new daily water bottles. Mortality and all signs of overt toxicity will be recorded on the day observed. The observations shall include, but are not limited to, evaluations for changes in appearance of skin and fur, eyes, mucous membranes, respiratory and circulatory system, autonomic and central nervous systems, somatomotor activity, and behavior. All animals will also be observed on the day of necropsy and any findings will be recorded.

For the positive control substance treated group (Group 2 only), individual clinical observations will be recorded approximately 1 hour following each dose administration for findings that are potentially related to treatment or that might change before the next scheduled observation. Additional observations may be necessary and will be documented in the study records.

13.3. Body Weights

Individual body weights will be recorded on Gestation Days 0-21 (daily) for animals assigned to the main and exposure assessment phases.

13.4. Water Consumption

Individual water consumption (by weight) will be recorded on Gestation Days 0-21 (daily) for animals assigned to the main and exposure assessment phases.

The mean amount of TCE received by each group of rats (test substance consumption) will be calculated upon completion of the study based on mean water consumption of each group and the target concentration of the test substance in water formulations. For consistency and ease of reporting, concentrations for each dose group will be referred to by the initial target

concentration as has been used in previously published reports.[NOTEREF _Ref504935597 \h * MERGEFORMAT]

13.5. Food Consumption

Individual food consumption will be recorded on Gestation Days 0-21 (daily) for animals assigned to the main phase. Food intake will be reported as g/animal/day and g/kg/day for each corresponding body weight interval of gestation.

Food consumption will not be recorded for animals assigned to the exposure assessment phase.

13.6. Deaths and Animals Euthanized in Extremis

Females not surviving until the scheduled euthanasia will be necropsied (as soon as possible upon discovery) and cause of death recorded, if possible. Rats not expected to survive to the next observation period (moribund) will be euthanized by carbon dioxide inhalation. The cranial, thoracic, abdominal, and pelvic cavities will be opened and the organs examined. The number and location of implantation sites and viable fetuses will be recorded. Corpora lutea will also be counted and recorded. Uteri which appear nongravid by macroscopic examination will be opened and placed in 10% ammonium sulfide solution for detection of early implantation loss.[6] Gross lesions will be preserved in 10% neutral-buffered formalin for possible future histopathologic examination. Carcasses from adult animals will be discarded. Viable fetuses will be euthanized by a subcutaneous injection of sodium pentobarbital in the scapular region. Recognizable fetuses will be examined externally and preserved in 10% neutral-buffered formalin.

Animals dying or euthanized *in extremis* (by carbon dioxide inhalation) that are assigned to the exposure assessment phase will have pregnancy status determined (by ammonium sulfide, if necessary). Viable fetuses will be euthanized by a subcutaneous injection of sodium pentobarbital in the scapular region. Carcasses of the dams and fetuses will be discarded.

13.7. Premature Deliveries

Females that deliver prematurely will be euthanized by carbon dioxide inhalation that day. The thoracic, abdominal, and pelvic cavities will be opened and the organs examined. The number and location of former implantation sites and viable fetuses will be recorded. Corpora lutea will also be counted and recorded. Gross lesions will be preserved in 10% neutral-buffered formalin for possible future histopathologic examinations. Carcasses from adult animals will be discarded. Viable fetuses or pups will be euthanized by a subcutaneous (scapular region) or intraperitoneal injection of sodium pentobarbital (as appropriate). Recognizable fetuses or pups will be examined externally and preserved in 10% neutral buffered formalin. Recognizable fetuses or pups aborted on GD 21 will be examined according to the fetal examination section (Section 15.2), if possible.

Females that deliver prematurely that are assigned to the exposure assessment phase will be euthanized by carbon dioxide inhalation that day and identified as gravid. Viable pups will be

euthanized by an intraperitoneal injection of sodium pentobarbital. Carcasses of the dams and pups will be discarded.

14. LABORATORY EVALUATIONS (EXPOSURE ASSESSMENT PHASE)

14.1. Intervals

Dams: Gestation days 8, 12 and 21

Fetuses: Gestation Day 21

Commented [PSC7]: Removed verbiage pertaining to TCE concentration assessments throughout. Since TCA is not volatile, we don't need to use vacutainer tubes. Also, we are still checking on availability of Amber EDTA tubes, if not, samples will be protected from light be storage and transfer in closed coolers and with the use of aluminum foil.

14.2. Blood Collection Time Points

Dams (Gestation Day 8 and 12): A single blood samples will be collected from each dam between 0830 and 0930 hours.

Dams and Fetuses (Gestation Day 21): A single blood sample will be collected from each dam just prior to euthanasia. Immediately following blood collection, each dam will be euthanized by carbon dioxide inhalation and uteri which appear gravid by macroscopic examination will be removed for fetal blood collection. For any dams that initiate parturition prior to blood collection, blood samples will be still be collected, as scheduled on Gestation Day 21/Lactation Day 0. Delivered pups (Postnatal Day 0) belonging to these females will be bled in the same manner as the Gestation Day 21 fetuses.

14.3. Number of animals

Dams: Four (4) females/group assigned to the exposure assessment phase.

Fetuses: Four (4) litters ~~(pooled by litter)~~ per group from dams assigned to the exposure assessment phase. Blood will be pooled by litter, without regard to fetal sex.

14.4. Method/Route of Collection

Dams: via the jugular vein using the hand-held restraint method.

Fetuses: via cardiac puncture under isoflurane anesthesia. Delivered pups (Postnatal Day 0) belonging to any females that deliver prior to blood collection will be bled in the same manner as the Gestation Day 21 fetuses.

14.5. Target Blood Volume

Dams: 0.5 mL/animal/time point; samples will be transferred as rapidly as possible from the collection syringe into pre-chilled, uniquely labeled ~~amber vacutainer~~ tubes. Samples will be protected from light, to the extent possible.

Fetuses: As much blood as possible; blood will be pooled by litter regardless of sex. Samples will be transferred as rapidly as possible from the collection catheter/syringe into pre-chilled, uniquely labeled ~~amber vacutainer~~ tubes. Samples will be protected from light, to the extent possible.

14.6. Anticoagulant

~~Lithium Heparin(s) EDTA (amber vacutainer tubes)~~

14.7. Sample Handling and Plasma Preparation

Samples will be kept on wet ice, protected from light, following blood collection and through centrifugation, plasma collection, and storage. All samples will be centrifuged (approximately 3000 rpm [approximately 2056xg] for approximately 10 min) at approximately 4°C. Samples will be processed under amber light.

14.8. Aliquots

The maximum amount of plasma will be recovered and plasma will be transferred into new, uniquely-labeled amber polypropylene tubes.

14.9. Label Information

Samples, and/or accompanying paperwork, will include study number, dose group, animal number, Gestation Day interval, number of pups (in pooled samples), sample type, date and time of blood collection.

14.10. Sample Storage and Transfer

Commented [PSC8]: Removed verbiage pertaining to TCE concentration assessment

Also combined the Sample Storage and Sample Transfer Sections into 1 section, per current CRL protocol template.

Maternal and fetal ~~Plasma~~ plasma samples will be stored in a freezer set to maintain a target of -70°C until transferred to the Charles River Bioanalytical Chemistry Department for analysis for the assessment of TCA concentrations using a method being developed and validated on a concurrent study.[7] The time and date that the samples are placed in the freezer will be recorded.

Any remaining samples kept at Charles River will be discarded following acceptance of the bioanalytical results by the Study Director.

The plasma analysis report will be included as an appendix to the Charles River final report.

14.11. Disposition of Animals/Laparotomy

All exposure assessment phase rats will be euthanized by carbon dioxide inhalation following the last blood collection (GD 21). Uteri which appear gravid by macroscopic examination will be removed immediately for fetal blood collection and the dams will be identified as gravid. Uteri which appear nongravid by macroscopic examination will be opened and placed in 10% ammonium sulfide solution for detection of early implantation loss.[NOTEREF _Ref461106913 \h * MERGEFORMAT] Following blood collection, fetuses will be euthanized by decapitation. Carcasses of the dams and fetuses will be discarded without further examination.

~~14.12. Sample Transfer for Plasma Analysis~~

~~Plasma samples, an inventory list and documentation of actual blood collection times for each animal, will be transferred to the Charles River Bioanalytical Chemistry Department for assessment of TCE and TCA concentrations in maternal and fetal samples.~~

~~Any remaining samples kept at Charles River will be discarded following acceptance of the bioanalytical results by the Study Director.~~

~~The plasma analysis report will be included as an appendix to the Charles River final report.~~

~~14.13.~~ 14.12. **Exposure Assessment**

Commented [PSC9]: Removed verbiage pertaining to TCE concentration assessment

Plasma concentrations of ~~TCE and~~ TCA in maternal and fetal samples will be summarized and presented in the main report text. Based on the limited blood sampling, the analysis of exposure data will be limited to mean concentrations, by group, and maternal and fetal concentration ratios.

15. TERMINAL PROCEDURES – GESTATION DAY 21 (PRENATAL DEVELOPMENT PHASE)

15.1. Laparohysterectomy and Macroscopic Examination

Laparohysterectomy and macroscopic examinations will be performed blind to treatment group. All surviving rats will be euthanized by carbon dioxide inhalation on Gestation Day 21. The thoracic, abdominal, and pelvic cavities will be opened and the organs examined. The uterus of each dam will be excised and its adnexa trimmed. Corpora lutea will be counted and recorded. Gravid uterine weights will be obtained and recorded. The uterus of each dam will be opened and the number of viable and nonviable fetuses, early and late resorptions, and total number of implantation sites will be recorded, and the placentae will be examined. The individual uterine distribution will be documented using the following procedure: all implantation sites, including early and late resorptions, will be numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix and continuing from the proximal to the distal right uterine horn. Uteri which appear nongravid by macroscopic examination will be opened and placed in a 10% ammonium sulfide solution for detection of early implantation loss.[NOTEREF _Ref461106913 \h * MERGEFORMAT] Maternal tissues will be preserved for future histopathologic examination in 10% neutral-buffered formalin only as deemed necessary by the gross findings. Representative sections of corresponding organs from a sufficient number of controls will be retained for comparison, if possible. The carcasses will be discarded.

15.2. Fetal Examination

Fetal examinations will be conducted without knowledge of treatment group. All fetuses will receive an external examination. **Internal (visceral) examination will be limited to an examination of the heart and great and major blood vessels only.** Representative photographs of all cardiac and great and major blood vessel malformations, as appropriate, will

be included in the study records, for illustrative purposes only. In addition, representative photographs of a normal littermate, will also be included in the study records, as needed and as appropriate, for comparison, where possible. **Representative photographs of all malformations with comparison photographs of normal fetuses will be included in the final report, for illustrative purposes only.** Prenatal data (viable and nonviable fetuses, early and late resorptions, pre- and post-implantation loss, and the fetal sex distribution) will be presented on a group mean basis and additionally as proportional data (% per litter).

15.2.1. External

Each viable fetus will be examined in detail, sexed, weighed, and euthanized by a subcutaneous injection of sodium pentobarbital in the scapular region. Nonviable fetuses (the degree of autolysis is minimal or absent) will be examined, crown-rump length measured, weighed, sexed and tagged individually. The crown-rump length of late resorptions (advanced degree of autolysis) will be measured, the degree of autolysis recorded, a gross external examination performed (if possible), and the tissue will be discarded.

15.2.2. Visceral (Internal)

Fetuses will be examined for visceral cardiac anomalies by dissection in the fresh (non-fixed) state. The thoracic cavity will be opened and dissected using a technique described by Stuckhardt and Poppe[8] with the exception that internal examination will be limited to a thorough examination of the heart and great and major blood vessels only. **Any observed ventricular septal defects will be categorized by size (<1 mm, 1 to 2 mm, or >2 mm) and location (muscular or membranous).** The abdomen will be opened with the sole purpose of internal confirmation of the sex of all fetuses. All carcasses will be discarded following completion of internal examination.

16. STATISTICAL METHODS

All analyses will be two-tailed for significance levels of 5% and 1%. All statistical tests will be performed using a computer with appropriate programming as referenced below. Data from nongravid females will be excluded from calculation of means and from comparative statistics. The litter, rather than the fetus, will be considered as the experimental unit.

Comparative statistics will not be performed on in-life or necropsy data from exposure assessment phase animals.

Data for the positive control substance group will be compared to the control group using a two-sample t-test[9] to determine intergroup differences.

16.1. Maternal In-Life Data

Continuous data variables (maternal body weights [absolute and net], body weight gains [absolute and net], food, and water consumption of each interval) will be subjected to a parametric one-way analysis of variance (ANOVA).[10] If the results of the ANOVA are

significant ($p<0.05$), Dunnett's test[11] will be applied to the data to compare the test substance treated groups to the control group.

16.2. Laparohysterectomy Data

The group mean numbers of corpora lutea, implantation sites, viable fetuses, maternal gravid uterine weights and mean fetal weight (separately by sex, and combined) will be subjected to a parametric one-way analysis of variance (ANOVA) and Dunnett's test as described above.[NOTEREF _Ref459642388 \h * MERGEFORMAT],[NOTEREF _Ref459642350 \h * MERGEFORMAT] The mean litter proportions of prenatal data (% per litter of viable and nonviable fetuses, early and late resorptions, total resorptions, pre- and post-implantation loss, and the fetal sex distribution) will be subjected to the Kruskal-Wallis nonparametric ANOVA test[12] to determine intergroup difference. If the results of the ANOVA are significant ($p<0.05$), Dunn's test[13] will be applied to the data to compare the test substance treated groups to the control group.

16.3. Fetal Morphology Data

The mean litter proportion (% per litter) of total fetal cardiac malformations and developmental variations and of each particular visceral cardiac malformation or variation will be tabulated. The mean litter proportions of fetal cardiac malformations and developmental variations will be subjected to the Kruskal-Wallis nonparametric ANOVA test followed by Dunn's test (if appropriate), to compare the test substance treated groups to the control group, as described above.[NOTEREF _Ref459642436 \h * MERGEFORMAT],[NOTEREF _Ref459642446 \h * MERGEFORMAT]

17. MAJOR COMPUTER SYSTEMS - DATA ACQUISITION, ANALYSIS, AND REPORTING

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

Data for parameters not required by protocol, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by protocol and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

All computerized systems used for data collection during the conduct of this study have been validated (with the exception of Microsoft Office and GraphPad Prism® 2008); when a particular system has not satisfied all requirements, appropriate administration and procedural controls were implemented to assure the quality and integrity of the data. The actual version number will be specified in the report.

Critical Computerized Systems

Program/System	Description
Archive Management System (AMS)	In-house developed application for storage, maintenance, and retrieval of information for archived materials (e.g., lab books, study data, wet tissues, slides, etc.).

Program/System	Description
Bio Medic Data Systems (BMDS) Implantable Micro Identification™ (IMI-1000 or IMI-500)	Animal identification
Dionex Chromeleon® software, Varian MS Workstation® software, Agilent ChemStation® software, or Molecular Devices SpectraMax® software	Used for chromatographic data acquisition and quantitation
InSight® Publisher	Electronic publishing system (output is Adobe Acrobat, PDF).
Logbook™ ELN	System (Instem) used to document study events.
Master Schedule	Maintains the master schedule for the company.
MD5 Checksum Tool	Used to generate and verify MD5 checksums during the final report generation process to create a significant, permanent link between the electronic study report and the signature page.
Metasys DDC Electronic Environmental Control System	Controls and monitors animal room environmental conditions.
Microsoft Office 2010 or higher; GraphPad Prism® 2008	Used in conjunction with the publishing software to generate study reports.
Provantis Dispense™	Comprehensive system (Instem LSS Limited) to manage test materials, including receipt, formulation instructions, and accountability.
SAS®	Statistical (non-WTDMS™) analyses
Watson LIMS™	Laboratory Information Management System used for sample tracking, run planning, quantitation, and reporting results.
WIL Formulations Dispense System (WFDS)	In-house developed system for use in conjunction with Provantis Dispense™ to ensure proper storage and use of formulations.
WIL Metasys	In-house developed system used to record and report animal room environmental conditions.
WIL Toxicology Data Management System™ (WTDMS™)	In-house developed system used for collection and reporting of in-life and postmortem data.

Note: Version numbers of WTDMS™ programs used for the study are presented on the report data tables (reporting programs); version numbers and release dates are otherwise maintained in the study records and/or facility records.

18. AMENDMENTS AND DEVIATIONS

Changes to the approved protocol shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary protocol changes in advance with the Sponsor.

All protocol and SOP deviations will be documented in the study records. Deviations from the protocol and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

19. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, protocol, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to a Charles River archive. At least 1 year after issue of the Draft Report, the Sponsor will be contacted.

For work product shipped or generated by a test site, archiving will be conducted per test site SOPs and will be described in the test site report.

Unless otherwise indicated, any remaining clinical pathology, toxicokinetic, and/or analytical samples will not be archived, but will be discarded prior to issuance of the final report.

Any work product, including documents, specimens, and samples, that are required by this protocol, its amendments, or other written instructions of the Sponsor to be shipped by Charles River to another location will be appropriately packaged and labeled as defined by Charles River SOPs and delivered to a common carrier for shipment. Charles River will not be responsible for shipment following delivery to the common carrier.

20. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Testing Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

Reports should be finalized within 6 months of issue of the Audited Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Testing Facility unless other arrangements are made by the Sponsor.

21. ANIMAL WELFARE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (Code of Federal Regulations, Title 9), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* from the Office of Laboratory Animal Welfare,[14] and the *Guide for the Care and Use of Laboratory Animals* from the National Research Council.[15] The protocol and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by the Testing Facility Institutional Animal Care and Use Committee before the initiation of such procedures.

If an animal is determined to be in overt pain/distress, or appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons in accordance with the *American Veterinary Medical Association (AVMA) Guidelines on Euthanasia* and with the procedures outlined in the protocol.[16]

By approving this protocol, the Sponsor affirms that there are no acceptable non-animal alternatives for this study, and that it does not unnecessarily duplicate any previous experiments.

22. REFERENCES

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TESTING FACILITY APPROVAL

The signature below acknowledges Testing Facility Management's responsibility to the study as defined by the relevant GLP regulations.

_____Date:_____
Donald G. Stump, PhD, DABT
Senior Director, Toxicology
Testing Facility Management

The signature below indicates that the Study Director approves the study protocol.

_____Date:_____
Prägati Sawhney Coder, PhD, DABT
Director, Developmental and Reproductive Toxicology
Study Director

SPONSOR APPROVAL

The protocol was approved by the Sponsor by Email on 12-Apr-2018. The signature below confirms the approval of the protocol by the Sponsor Representative.

_____Date:_____

Christopher J. Bevan, PhD, DABT
Director, Scientific Programs
Halogenated Solvents Industry Alliance, Inc.
Sponsor Representative

Comparison of NTP OHAT and USEPA TSCA Study Quality Criteria — Trichloroethylene (TCE) and Congenital Heart Defects (CHDs) as a Case Study

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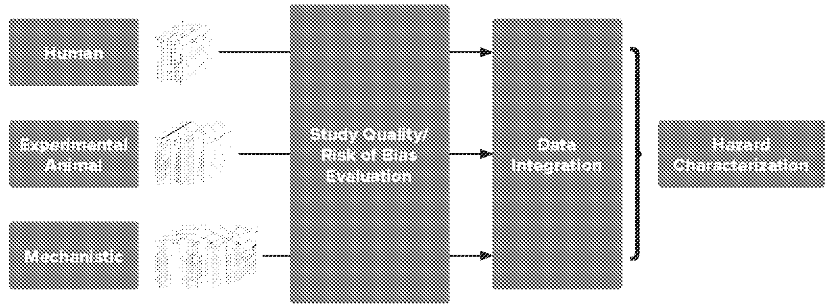
Poster #: P306
Abstract #: 2801



Introduction

- Current TCE regulations are based on a single experimental animal study reporting an association between gestational exposure to trichloroethylene (TCE) and the development of congenital heart defects (CHDs) in offspring. This TCE-CHD association is controversial as it was not observed in the 11 other TCE developmental animal toxicology studies, including GLP studies specifically designed to repeat the single study that reported an association.
- Globally, systematic review is being implemented to facilitate hazard and risk evaluations. As part of developing best practices, various critical appraisal tools are being designed or refined to accommodate evidence bases which include many different types of studies (i.e., experimental animal, *in vitro*, and observational studies).
- Existing critical appraisal tools generally assess the internal validity of a study, as assessed by the risk of bias (RoB). With increasing use in toxicology, it is being recognized that other aspects of study quality are important on the individual study level (e.g., external validity or relevance). Some such aspects are considered in a newly released study quality tool issued by the USEPA-OPPT to facilitate the TSCA risk assessment systematic review process (USEPA, 2018). This tool is unique as it includes study quality metrics for mechanistic studies (e.g., *in vitro* studies).
- To date, only subsets of the TCE-CHD literature (human, animal) have been subjected to formal systematic critical appraisal (Wikoff et al., 2018).

Objective

To assess the impact of various systematic critical appraisal tools in the evaluation of the full evidence base (human, animal, and mechanistic data) for TCE-CHD.

Methods

Development of TCE-CHD Evidence Base (Literature Search):

- Using ad hoc searching and reference chasing, epidemiology, animal toxicology, and mechanistic studies were identified from recent comprehensive reviews conducted systematically (Makris et al., 2016; Wikoff et al., 2018). Additional PubMed and Embase searches were also conducted using the same search syntax utilized to capture relevant studies published since Wikoff et al. (2018). Searches were executed October 30, 2018.
- Mechanistic studies were categorized based on the assay type(s) to accommodate the TSCA study quality tool: *in vivo* (animals exposed), *in vitro* (cell culture, *in ovo*, *ex ovo*, *ex vivo*).

Critical Appraisal Tools (Table 1)

- **OHAT RoB:** Two study categories (animal and human) with defined, and reviewer refined, criteria for assessing bias (low, high; definite, probable). The RoB for the TCE-CHD human and animal literature is based on Wikoff et al. (2018).
- **TSCA Study Quality Evaluation:** Three study categories (human, *in vivo*, and *in vitro*) with specific evaluation and scoring metrics, each metric being scored on 1 of 4 criteria; overall study quality was determined by weighted scoring calculations and categorizations.
- **SciRAP:** Used in this effort to compare TSCA *in vitro* study quality results. Criteria evaluate the reporting and methodological quality, and relevance of *in vivo* and *in vitro* studies. Tool calculates a score for each category based on reviewer selection of several criteria.

Study Quality Assessment Procedure

- Pilot assessments: Independent review of subset of studies/experiments by two analysts for each of the three study categories. Decisions, interpretations, and refinements were documented.
- Quality assessments were conducted by two scientists with experience reviewing epidemiology (MS, JB), experimental animal (SF, JU), and mechanistic (GC, JU) studies. In cases of conflict, a third scientist (DW) was consulted to facilitate a consensus solution.

Data Integration and Body of Evidence Assessment

- Integration approach is based on OHAT (2015) and builds on that from Wikoff et al. (2018) to include mechanistic data and consider data quality output as determined by various appraisal tools.
- For mechanistic data, confidence-rating factors proposed by OHAT (2015) were considered: magnitude/potency, dose-response, consistency, directness, validity. Consideration was also given to the biological plausibility of data in the context of an adverse outcome pathway construct (which also relies on data from animal and human evidence streams to characterize adverse outcomes; in the case of TCE-CHD, adverse outcomes are limited as the majority of data suggest lack of such).

Table 1. Critical Appraisal Tool Study Quality Domains/Metrics

Study Type	NTP-OHAT RoB (2015)	USEPA OPPT TSCA (2018)	SciRAP (2018)
Epidemiology	**7 Questions covering 6 Bias Domains:** 1. Selection Bias (1) 2. Confounding Bias (1) 3. Attrition/Exclusion Bias (1) 4. Detection Bias (2) 5. Selective Reporting (1) 6. Other Bias (1 - covers statistics)	**15 Metrics covering 5 Study Elements:** 1. Study Participation (3) 2. Exposure Characterization (3) 3. Outcome Assessment (2) 4. Potential Counfounding/Variable Control (3) 5. Analysis (4)	[Not covered]
Animal Toxicology	**9 Questions covering 6 Bias Domains:**[*] 1. Selection Bias (2) 2. Performance Bias (2) 3. Attrition/Exclusion Bias (1) 4. Detection Bias (2) 5. Selective Reporting (1) 6. Other Bias (1 - covers statistics)	**24 Metrics covering 7 Study Elements:** 1. Test Substance (3) 2. Test Design (3) 3. Exposure Characterization (6) 4. Test Organism/Test Model (3) 5. Outcome Assessment (5) 6. Confounding/Variable Control (2) 7. Data Presentation and Analysis (2)	**53 Criteria covering 3 Study Elements:** 1. Reporting Quality (30) 2. Methodological Quality (18) 3. Relevance (5) [Not utilized in the current effort]
In vitro	[Not covered]	**25 Metrics covering 7 Study Elements:** 1. Test Substance (3) 2. Test Design (4) 3. Exposure Characterization (6) 4. Test Model (2) 5. Outcome Assessment (4) 6. Confounding/Variable Control (2) 7. Data Presentation and Analysis (4)	**42 Criteria covering 3 Study Elements:** 1. Reporting Quality (23) 2. Methodological Quality (15) 3. Relevance (4)

[*] OHAT RoB guidelines encourages reviewers to expand/modify/split questions to make relevant to PECO. For TCE-CHD case study, Wikoff et al. (2018) split 9 animal questions out to 14 questions.

Results

TCE-CHD Evidence Base

Table 2. TCE-CHD Literature

Study Type	# Relevant Published Studies	# Study Quality Assessments	
Epidemiology	10	9	
Animal Toxicology	11	12	
Mechanistic	22	Total: 68 [Avg: 3.1 Assays/Study]	
		In vivo: 5 In vitro (cell culture): 26 In vitro (in ovo): 21 In vitro (ex ovo): 3	In vitro (ex vivo): 7 In vitro (zebrafish): 5 Unknown model: 1
Total	43	89	

Critical Appraisal of Epidemiological Data

- Overall study quality as assessed by the various tools was low for the epidemiological literature. Appraisal outcome was driven by limitations in study design and reporting particularly related to study participation, exposure assessment, and confounding.
- **Conclusion:** The nine studies comprising the human evidence base for TCE-CHD are of very limited study quality for risk assessment.

Table 3. Critical Appraisal of Human Studies Relevant to TCE-CHD Risk Assessment

Reference	Study Design	TSCA designation[1]	OHAT RoB Designation[2]
Epidemiology Studies			
Bove et al. (1995)/Bove (1996)	Cross-sectional (assumed exposure via public water)	Unacceptable (2x "4" scores)	Tier II
Brender et al. (2014)	Case-control (assumed exposure via air)	Unacceptable (1x "4" scores)	Tier II
Forand et al. (2012)	Ecological/Cross-sectional (assumed exposure via air)	High Quality (score=1.5)	Tier II
Gilboa et al. (2012)	Case-control (assumed exposure via air)	Unacceptable (1x "4" scores)	Tier II
Goldberg et al. (1990)	Pseudo-case-control (assumed exposure via public water)	Unacceptable (3x "4" scores)	Tier III
Lagakos et al. (1986)	Cross sectional (assumed exposure via public water)	Unacceptable (6x "4" scores)	Tier II
Ruckart et al. (2013)	Case-control (assumed exposure via public water)	Unacceptable (2x "4" scores)	Tier III
Tola et al. (1980)	Cohort (assumed exposure via air)	Unacceptable (9x "4" scores)	Tier II
Yauck et al. (2004)	Case-control (assumed exposure via air)	Unacceptable (4x "4" scores)	Tier II

[1] For OPPT scores, "high quality" studies <1.7, "medium quality" studies <2.3 and ≥1.7, "low quality" studies ≥2.3; any study with at least one metric score = 4 is automatically of "unacceptable quality".
[2] OHAT RoB Tiers as evaluated and reported in Wikoff et al. (2018)

Critical Appraisal of Experimental Animal Data

- Overall study quality as assessed by the various tools was medium to high for the experimental animal research. Appraisal outcome was largely driven by well reported and appropriate study design, consistent experimental conditions, and valid outcome methodologies.
- The Dawson et al. (1993)/Johnson et al. (2003) rat drinking water study was characterized as unreliable (poor study quality; high internal bias) by both OHAT and TSCA tools; common issues related to lack of concurrent controls, multiple vehicles within study groups, and unvalidated outcome assessment method.
- **Conclusion:** The majority of the animal evidence base for TCE-CHD [sans Dawson et al. (1993)/Johnson et al. (2003)] are amenable for risk assessment.

Table 4. Critical Appraisal of Animal Toxicology Studies Relevant to TCE-CHD Risk Assessment

Reference	Study Design	TSCA designation[1]	OHAT RoB Designation[2]
Oral Studies			
Cosby and Dukelow (1992)	Mouse - oral gavage GD 1-5, 6-10, or 11-15	Medium Quality (score=2.1)	Tier II
Dawson et al. (1993)/Johnson et al. (2003)	Rat - drinking water GD 1-22	Unacceptable (2x "4" scores)	Tier III
Fisher et al. (2001)	Rat - oral gavage GD 6-15	High Quality (score=1.5)	Tier II
Narotsky and Kavlock (1995)	Rat - oral gavage GD 6-19	Medium Quality (score=1.9)	Tier II
Narotsky et al. (1995)	Rat - oral gavage GD 6-15	Medium Quality (score=1.9)	Tier II
Inhalation Studies			
Carney et al. (2006)	Rat - whole body 6 hr/d, GD 6-20	High Quality (score=1.4)	Tier I
Dorfmueller et al. (1979)	Rat - whole body 6 hr/d, GD 1-20	Medium Quality (score=1.8)	Tier I
Hardin et al. (1981)a	Rat - whole body 7 hr/d, GD 1-19	High Quality (score=1.4)	Tier II
Hardin et al. (1981)b	Rabbit - whole body 7 hr/d, GD 1-22	High Quality (score=1.4)	Tier II
Healy et al. (1982)	Rat - whole body 4 hr/d, GD 8-21	Medium Quality (score=2.0)	Tier II
Schwetz et al. (1975)a	Rat - whole body 7 hr/d, GD 6-15	Medium Quality (score=1.8)	Tier I
Schwetz et al. (1975)b	Mouse - whole body 7 hr/d, GD 6-15	Medium Quality (score=1.8)	Tier I

[1] For OPPT scores, "high quality" studies <1.7, "medium quality" studies <2.3 and ≥1.7, "low quality" studies ≥2.3; any study with at least one metric score = 4 is automatically of "unacceptable quality".
[2] OHAT RoB Tiers as evaluated and reported in Wikoff et al. (2018)

Critical Appraisal of Mechanistic Datasets

- Pilot study of 10 experimental datasets using TSCA demonstrated that five study metrics commonly differentiated studies; these were defined as "Key Metrics." (**Table 5**)
- Quality rankings based on the TSCA tool varied by study model (**Figure 1**).
- Aspects that commonly differentiated studies within the TSCA tool included reporting on the preparation and storage of the test substance (Metric 8), elements of data analysis (Metrics 22 and/or 23), and reporting on cytotoxicity (Metric 24, only relevant to cell culture experiments) (**Figure 2**).
- Study quality categorizations were overall similar for the subset of experiments also assessed using SciRAP (**Table 6**).
- **Conclusion:** The majority of the mechanistic studies are not reliable for risk assessment. Traditional assessment parameters (e.g., magnitude, consistency) were not sufficient to facilitate conclusions for mechanistic data. Consideration of the type of outcome assessed (e.g., gene expression, *in ovo* development), the study model (e.g., chicken eggs, rat whole culture embryos, zebrafish larvae, human embryonic stem cells), as well as the plausibility of findings in a biological construct (e.g., adverse outcome pathway type of construct) were critical to integrating the evidence. The few mechanistic studies that were of sufficient quality were limited in their applicability due to heterogeneous models of questionable relevance to human physiology and exposure timing/dosing. Furthermore, the outcomes from these remaining studies were also inconsistent as it relates to outcome observations in mammalian species.

Table 5. Key Metrics Identified using TSCA Study Quality Metrics for TCE-CHD In Vitro Experiments

Metric No.	Metric Title	Metric Description
8	Preparation and Storage of Test Substance	Did the study characterize preparation of the test substance and storage conditions? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability and solubility (if applicable)?
11	Exposure Duration	Was the exposure duration (e.g., minutes, hours, days) reported and appropriate for this study type and/or outcome(s) of interest?
16	Outcome Assessment Methodology	Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints and timing of assessment) sensitive for the outcome(s) of interest (e.g., measured endpoints that are able to detect a true effect)?
22	Data Analysis	Were statistical methods, calculations methods, and/or data manipulation clearly described and appropriate for dataset(s)?
24	Cytotoxicity	Were cytotoxicity endpoints defined, if necessitated by study type, and were methods for measuring cytotoxicity described and commonly used for assessments?

Figure 1. TCE-CHD Mechanistic Studies by Model Type and Study Quality Category Based on TSCA Systematic Review Guidelines

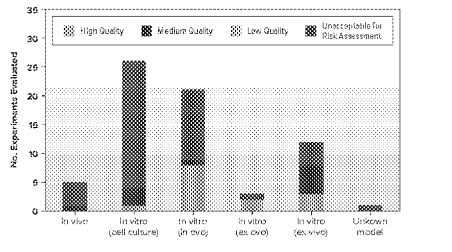


Figure 2. TSCA Study Quality Metrics Scored "Unacceptable" Across TCE-CHD Mechanistic Evidence Base

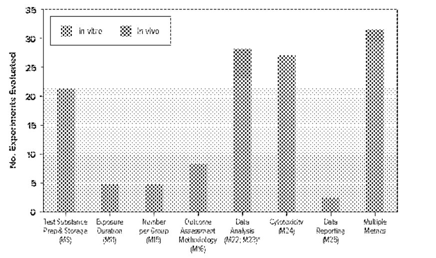


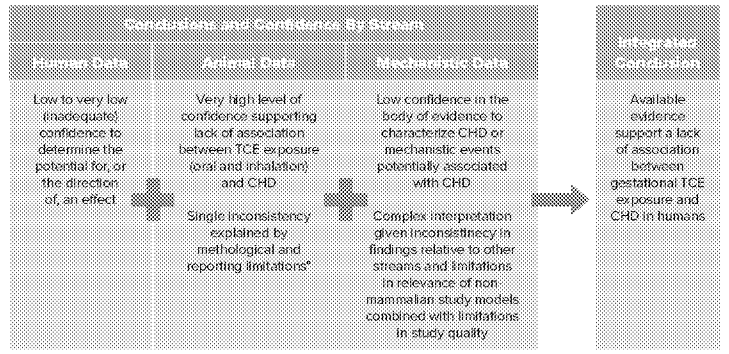
Table 6. Comparison of In Vitro Study Quality Evaluation Tools

Study	Experimental Model & Endpoint	Study Quality Evaluation Outcome: TSCA	Study Quality Evaluation Outcome: SciRAP
Drake et al EHP (2006)	In ovo: Level of apoptosis in atrioventricular cushion and outflow tract sections of HH24 staged chick embryo hearts	**Score:** 1.5 **Interpretation:** High Quality Study **Consequence:** Retain in TCE-CHD evidence base for risk assessment	**Reporting Quality Score:** 79 out of 100 **Methodological Quality Score:** 85 out of 100 **Consequence:** None defined
Harris et al (2018)	In vitro: Protein activity in transformed human liver cell line	**Score:** Not calculated; multiple metrics scored =4 **Interpretation:** Unacceptable for risk assessment **Consequence:** Remove from evidence base for TCE-CHD risk assessment	**Reporting Quality Score:** 90 out of 100 **Methodological Quality Score:** 50 out of 100 **Consequence:** None defined
Selmin et al (2005)	In vitro: Gene transcription levels in transformed rat heart cell line	**Score:** Not calculated; multiple metrics scored =4 **Interpretation:** Unacceptable for risk assessment **Consequence:** Remove from evidence base for TCE-CHD risk assessment	**Reporting Quality Score:** 43 out of 100 **Methodological Quality Score:** 46 out of 100 **Consequence:** None defined

Body of Evidence Assessment

- Overall, there is higher confidence in the animal studies compared to human studies or mechanistic studies, based on the output of the various critical appraisal tools.
  1. Notably, the Dawson et al. (1993)/Johnson et al. (2003) study was determined to be unreliable by both appraisal tools. This emphasizes the likelihood that shortcomings in methodological and reporting aspects can explain the inconsistent findings of this study relative to the other 11 animal studies in the evidence base.
- Data Integration (**Figure 3**): Considered together, the available human, animal, and mechanistic study data support a lack of association between gestational TCE exposure and CHDs.
  1. Human studies → Low confidence in evidence stream associating in utero TCE exposure with increased risk of CHDs (similar to conclusions using OHAT RoB tool): Only a single study met TSCA quality criteria, and that was an ecological study.
  2. Animal studies → High confidence in evidence stream for TCE-CHD null hypothesis (i.e., no association of gestational TCE exposure and increased CHD risk): Only study to show dose response effect failed to meet TSCA study quality criteria.
  3. Mechanistic studies → Low confidence in evidence stream: inconsistency and relevance of outcomes and non-mammalian models are difficult to interpret given the lack of effect in experimental animal models (mammalian).

Figure 3. Data Integration: Evidence Stream Summaries and Integrated Conclusion



Conclusions

- Despite differences in the critical appraisal tools employed herein, consideration of study quality resulted in similar findings: the experimental animal studies offer the highest level of confidence. Both approaches deemed the Johnson et al. (2003) rat study unreliable for using in quantitative risk assessment.
- Given the consistent findings of experimental animal studies demonstrating a lack of TCE-CHD relationship, the utility of assessing and integrating the mechanistic data is limited, particularly considering the complexity of interpreting the relevance of diverse models (e.g., non-mammalian) and exposure paradigms (e.g., direct *in vitro* cell culture exposures extrapolate to high exposure concentrations in humans) utilized in a risk assessment context. Notably, in contrast to the rodent data, non-mammalian models (*in ovo*, zebrafish) provide the strongest evidence supporting TCE-CHD association. These models are heuristic tools useful for hypothesis development but are of highly questionable relevance for human health risk assessment.
- The use of multiple tools for evaluating the quality of study data across evidence bases can increase confidence in systematic review findings and provide an understanding of the practical application of available approaches.

Acknowledgements This work was funded by the American Chemistry Council.

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APPENDIX 1 (CORRECTED)

HSIA halogenated solvents industry alliance, inc.

MEMORANDUM

To: Docket EPA-HQ-OPPT-2016-0163

From: Faye Graul
Executive Director

Date: March 16, 2017

Subj: Trichloroethylene Drinking Water Study

Attached please find a copy of Protocol Number WIL-459501 titled An Oral (Drinking Water) Study of the Effects of Trichloroethylene (TCE) on Fetal Heart Development in Sprague Dawley Rats. The Protocol was signed on October 6, 2016 and the in-life portion of the study was conducted during October and November, 2016. Unfortunately, the concentrations of TCE measured in the drinking water solutions were found to be below the acceptable target range of 100% ± 10%, invalidating the study. The laboratory is conducting additional studies to identify the source of the deviations and the study will be rerun as soon as the dosing methodological issues are resolved and scheduling permits.

3033 Wilson Boulevard, Suite 700 • Arlington, VA 22201
www.hsia.org

WIL RESEARCH

5 August 2016
Proposal: 15.04279

Proposal for Halogenated Solvents Industry Alliance

Proposal provided by:
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Scientific Director
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E-mail: eddie.sloter@wilresearch.com

Proposal Summary

Study	Base Study Fee	Optional			Total Study Fee	
		AC	BioAC	TK Report		Authorized
A (5-Group) Prenatal Developmental Toxicity Study of TCE Administered by Drinking Water in Sprague Dawley Rats	$168,000	$12,400	$15,730	$4,100	$200,230	X
Analytical Validation, Homogeneity, and Stability Study of the Analyte in Aqueous Formulations	$24,160	-	-	-	$24,160	X
Development and Testing of an LC-MS/MS Method for the Quantification of Test Article (TCE) and a Major Metabolite (TCA) in Rat Plasma	$11,050	-	-	-	$11,050	X
Validation of an LC-MS/MS Method for the Quantification of Test Article in Rat Plasma	$28,750	-	-	-	$28,750	X

***Fee and Payment Schedules are subject to credit approval.**

Authorization Statement

Halogenated Solvents Industry Alliance ("Sponsor") hereby awards the above described proposal (the "Proposal") to WIL Research Laboratories, LLC ("WIL") (each a "Party"), and requests WIL to proceed with the necessary activities to initiate these Services, including but not limited to, Protocol development, Study room reservation, and definitive scheduling of Services.

This Proposal, the performance of Services, and each Party's obligations herein are governed by and subject to the WIL Research Laboratories LLC General Terms and Conditions attached hereto (the "General Terms and Conditions"). The General Terms and Conditions are hereby incorporated by reference to this Proposal in their entirety. By executing below, Sponsor acknowledges and represents, and the undersigned person executing this Proposal on behalf of Sponsor certifies, that such person has read and Sponsor agrees to the provisions set forth in the General Terms and Conditions.

This Proposal (including the relevant Protocol), together with the General Terms and Conditions and the Confidentiality Agreement between the Parties dated [08/08/14], constitutes the entire agreement (the "Agreement") between the Parties with respect to the subject matter contained herein. There are no oral or written promises, terms, conditions, or obligations other than those contained in this Agreement. This Agreement supersedes all prior negotiations, representations or other agreements, either written or oral, between the Parties on the subject matter related herein. No modification or waiver of the provisions of this Proposal, the General Terms and Conditions or the Confidentiality Agreement shall be valid or binding on either Party unless agreed to in writing by each Party.

In the event the terms of this Proposal or any other agreement between the parties hereto contradict any provision of the General Terms and Conditions, the General Terms and Conditions shall control unless expressly agreed to in writing by each Party herein.

Any notices given hereunder shall be sent by fax or email, with a confirmation copy sent via overnight courier to the following addresses (or such other address as a party may designate as a notice address in a written notice to the other party) and shall be deemed received when delivered (or if received on a weekend or holiday, on the next business day thereafter) as follows:

If to Sponsor: Name: John Bell
Title: Director, Scientific Programs
Company: Halogenated Solvents Industry Alliance, Inc.
Address: 3033 Wilson Boulevard
Suite 700
Arlington, VA 22201
Phone: 202 286 6464
Email: jbell@hsia.org

If to WIL: John Maxwell
Vice President
WIL Research Laboratories, LLC
1407 George Road
Ashland, OH 44805
Phone: (419) 289-8700
Email: john.maxwell@wilresearch.com

With a copy to: Corporate Counsel
WIL Research Laboratories, LLC
8025 Lamon Avenue
Skokie, IL 60077
Email: jon.galli@wilresearch.com

By executing this document Sponsor understands, acknowledges and agrees to the financial responsibility for all costs and expenses in accordance with this Proposal including those incurred by WIL in preparation of the Study. Any modification that requires an increase in cost subsequent from the effective date of this Proposal will be adjusted through a Study Modification.

Signature of Authorized Sponsor Representative — Date: August 8, 2016

Name: John Bell, Ph.D., DABT

Title: Director, Scientific Programs

Company: Halogenated Solvents Industry Alliance, Inc.

Company Address: Suite 700

3033 Wilson Boulevard

Arlington, VA 22201

Email Address (invoices will only be sent as a PDF to this email address):

jbell@hsia.org

A (5-Group) Prenatal Developmental Toxicity Study of TCE Administered by Drinking Water in Sprague Dawley Rats
Compliance: GLP, OECD
Guidelines: Modified OECD 414

Group	Toxicology Animals (145)	
	Toxicology Females (150)	Maternal TK (20)
1	25	4
2	25	4
3	25	4
4	25	4
5	25	4
6	25	-

Objective:	To detect potential adverse effects on the pregnant female and on the development of the embryo and fetus consequent to exposure of the female starting the day after mating (Gestation Day 1) through implantation and gestation until one day prior to expected parturition.
Animals[3]:	Female Sprague Dawley Rats Crl:CD(SD) 170 animals on study, 212 animals ordered Untreated sexually mature males of the same strain and source will be used to induce pregnancies.
Groups:	1 control group, 4 test article-treated groups and 1 positive control group.
Dose Levels[3]:	Highest dose will be 1100 ppm in drinking water based on a previous study conducted by Johnson et al.
Test Substance Preparation:	Prepared at a frequency consistent with established stability.
Sampling of Formulations:	From the first and last preparations. Samples analyzed at WIL Research (optional).
Test Substance Administration:	Via drinking water (glass water bottles) from gestation day 1 until the day of scheduled necropsy at the end of gestation, inclusively. Day evidence of mating is confirmed is gestation day 0. Group 6 (positive control group) dosed via oral gavage from Gestation Day 6-15, inclusively.
Viability Observations:	Twice daily observations for moribundity and mortality.
Clinical Observations:	Once daily.
Body Weights:	Toxicology Animals: Gestation days 0-20 (daily). Toxicokinetic Animals: Gestation days 0-20 (daily).
Food Consumption:	Toxicology Animals: Gestation days 0-20 (daily). Toxicokinetic Animals: Not recorded.
Toxicokinetics:	Maternal TK Phase – Blood samples collected from each dam on GD 8, GD 16 and again at the end of the administration period (GD 20) from 4 maternal toxicokinetic animals/group/time point at a single time point (60 maternal samples). Samples can be analyzed at WIL Research (optional). Fetal TK – Immediately following the final maternal tk blood collection on GD 20, each dam will be euthanized and fetal blood will be collected from the umbilical vessel of each fetus and pooled by litter (20 pooled fetal samples). Samples can be analyzed at WIL Research (optional).
Scheduled Laparohysterectomy:	Toxicokinetic Animals: Gestation day 20; Determination of pregnancy status only and fetal blood collected as required. Toxicology Animals: Gestation day 20; Examination of uterine contents: determination of pregnancy status, gravid uterine weights, gross evaluation

of placenta and count of corpora lutea, implantation sites, early and late resorptions and viable and nonviable fetuses.

Fetal Observations: External and fresh visceral examinations of all viable fetuses for developmental variations and malformations, sex ratios and body weights. The carcass of each fetus will be preserved and retained for possible future skeletal evaluation.

Quality Assurance: The study will be conducted in compliance with Good Laboratory Practice (GLP) standards and will be monitored by the Quality Assurance Unit.

Reports: Audited Draft Report and Final Report.

Archiving: For a period of six months after study completion.

5-Group Base Study Fee (Full Fetal Visceral Evaluations) [1] $166,000

Optional Support Fees:

Analytical Chemistry (AC): [2] $3,400/set

Concentration determination (1st preparation with concurrent homogeneity):	$3,400
Resuspension homogeneity (1 interval):	$3,400
Concentration determination (last preparation):	$3,400
Sample analysis report:	$2,200
Total Study-specific AC:	$12,400

Bioanalytical Chemistry (BioAC): [4]

Sample analysis - 80 samples @ $85/sample (minimum batch 100 samples):	$8,500
Dilution repeats - 30 samples @ $85/sample[5] (estimated 10% of samples; minimum batch 30 samples):	$2,550
Incurred sample reanalysis - 8 samples @ $85/sample:	$680
Report Fee[6]:	$4,000
Total Study-specific BioAC:	$15,730

Toxicokinetic Report:

Preparation of a toxicokinetic report from the maternal and fetal exposure data for a single analyte and single dose route. Preliminary toxicokinetic results will be available upon request and will typically be provided within two business days of availability of bioanalytical data.

TK Report: $4,100

1. Final price depends on the technical details in the final protocol and will be set forth in a Work Order. Base study fee is exclusive of analytical and bioanalytical chemistry support and toxicokinetic evaluation. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.
2. A minimum of 20 litters per group is recommended in this guideline.
3. Studies that do not establish a maternal NOAEL may be acceptable under this guideline.
4. These fees are considered estimates until the method has been developed. The fee for method development and validation is not included. Upon completion of the method development, the sponsor will be notified if different analysis fees apply. The costs also assume typical sample processing as well as standard analytical detection will be sufficient. Long processing procedures, long analytical run times, and mass spectrometric detection will result in an increased fee.
5. These fees are considered estimates. Additional samples and dilution repeats beyond 10% will be charged at a rate of $85/sample. The Sponsor will be notified in writing, prior to application of any such fees.
6. A report fee will be waived if there are ≥ 150 samples analyzed.

Fee and Payment Schedule:
20% upon signature of the Proposal
40% 45 days prior to animal arrival
30% upon completion of in-life
10% upon issuance of Draft Report

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

back to Proposal Summary

Analytical Validation, Homogeneity, and Stability Study of the Analyte in Aqueous Formulations
Compliance: GLP

Development and validation of a method for the determination of analyte concentration in aqueous formulations:

Method development usually includes (but is not limited to) the following activities: (1) investigation of potential solubility limitations; (2) the analysis of standards prepared in an appropriate solvent to establish chromatography, including retention times, resolution, and to check proportionality of response; (3) the analysis of the analyte prepared in the matrix to confirm the presence or absence of interferences, to evaluate potential stability limitations, and to evaluate response proportionality. Method development will be billed at a rate of $260/hour and will not exceed the amount proposed without sponsor approval.

Validation will be conducted using the current WIL SOP guidelines for the assessment of system suitability, method specificity/selectivity, intra- and inter-session method calibration acceptability, intra- and inter-session method accuracy and precision, ruggedness, and processed sample stability. A minimum of three validation sessions will be conducted. All laboratory work associated with validations will be conducted in accordance with applicable GLP regulations.

Homogeneity and stability assessment of analyte in aqueous formulations:

Testing includes the assessment of test article homogeneity in formulations spanning the range of concentration anticipated on future studies. In addition, resuspension homogeneity and stability will be assessed following a single storage duration. Additional stability time-points can be added for an additional fee. All laboratory work associated with sample analysis will be conducted in accordance with applicable GLP regulations.

Quality Assurance: The study will be conducted in compliance with Good Laboratory Practice (GLP) standards and will be monitored by the Quality Assurance Unit.

Reports: Audited Draft Report and Final Report.

Archiving: For a period of six months after study completion.

Summary of Fees:

Method Development (up to 16 hours):	$4,160
Method Validation in Aqueous Formulations: [2]	$11,000
Homogeneity and Stability Assessments in Aqueous Formulations: [2]	$6,800
Analytical Report:	$2,200
Base Fee [1]	$24,160

1. Final price depends on the technical details in the final protocol and will be set forth in a Work Order. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.
2. These fees are considered estimates until the method has been developed. Upon completion of the method development, the sponsor will be notified if different analysis fees apply. The costs also assume that typical sample processing as well as standard analytical detection will be sufficient. Long processing procedures, long analytical run times, and mass spectrometric detection will result in an increased fee.

Fee and Payment Schedule:
50% upon signature of the Proposal
40% upon completion of analysis
10% upon issuance of Draft Report

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

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Development and Testing of an LC-MS/MS Method for the Quantification of Test Article (TCE) and a Major Metabolite (TCA) in Rat Plasma
Compliance: Non-GLP

Development:	A fit-for-purpose LC-MS/MS method will be developed for the quantification of test article and one major metabolite in rat plasma. Appropriate chromatographic, mass spectrometric, and sample extraction procedures will be developed to achieve the sensitivity and specifications needed to support non-clinical studies of the test article.
Testing:	Once a suitable method has been developed, testing will be conducted that will include quantifying standards, quality control samples, and blanks to estimate the sensitivity, linearity, accuracy, and reproducibility of the procedure, and to ensure that the proper concentration range and conditions are selected prior to validation or analysis of study samples (as applicable). WIL Research will provide the Sponsor with timely updates on progress.
Quality Assurance:	The study will not be monitored or audited by the Quality Assurance Unit.
Archiving:	For a period of six months after study completion.

Summary of Fees:

Development and Testing [1,2,3];	
24 hours @ $270/hour:	$6,480
Pre-Validation Testing 16 hours @ $270/hour:	$4,320
Materials:	$250
Base Study Fee [4]	$11,050

1. Method development and pre-validation will be billed at a rate of $270/hr. These activities will not be audited.
2. Species-specific plasma will be purchased from commercial sources and will be used as the blank (control) matrix. Estimated cost includes up to 100 mL of rat plasma.
3. The Sponsor will supply or reimburse for the test article(s) and suitable internal standard(s) (all with % purity ≥ 98%). Surcharges may apply for supplies that run outside the normal budget for this work.
4. Final price depends on the technical challenges encountered; additional time beyond that estimated above may be required; the Sponsor will be contacted for approval of any additional work. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.

Fee and Payment Schedule:
50% upon signature of the Proposal
50% upon completion of analysis

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

Back to Proposal Summary

Validation of an LC-MS/MS Method for the Quantification of Test Article in Rat Plasma
Compliance: GLP

Validation:	Validation will be performed according to the FDA "Guidelines for Bioanalytical Method Validation" and 21 CFR Part 58, Good Laboratory Practice for Non-Clinical Laboratory Studies (revised as of April 1, 2007). Testing will include a minimum of 3 runs of matrix standard curves, along with at least 4 QC concentrations (LLOQ, low, medium, high) and at least 18 replicates total at each concentration. Intra-assay and inter-assay precision and accuracy of the QC samples will be determined. Validation will also include evaluation of linearity and limit of quantification, reproducibility, dilution effect, recovery, selectivity, carryover and processing, freeze-thaw, whole blood, and stock solution stability.
Stability:	All plasma stability evaluations will be performed at the low, high, and dilution QC levels. Long-term frozen storage stability testing at one time point and at one temperature is included in the validation fee.
Additional Fees:	Additional fees, $4,500/occasion, may be applied if additional stability time points/temperatures are requested by the Sponsor.
Protocol:	A protocol will be prepared by WIL Research for the validation. The Sponsor and/or Sponsor's representative will review the draft protocol and approve the final protocol.
Quality Assurance:	The study will be conducted in compliance with Good Laboratory Practice (GLP) standards and will be monitored by the Quality Assurance Unit.
Reports:	An audited draft validation report will be prepared by WIL Research and the Sponsor will be given time to review and comment on the report before it is finalized. The final bioanalytical procedure will be provided with the validation report. Requests for specific formatting for protocols and/or reports or multiple revisions may incur additional fees.
Archiving:	For a period of six months after study completion.

Summary of Fees:

Validation for Quantification [1,2,3]

Validation:	$28,000
Additional stability time points @ $4,500/time point:	TBD
Materials:	$750
Base Study Fee [4]	$28,750

1. The validation fee assumes quantification of a single analyte and is considered an estimate until the method has been developed. Upon completion of the method development, the sponsor will be notified if the base study fee will change. The final validation fee is dependent upon, but not limited to the suitability of the IS compound, LC run time, complexity and number of extractions, and other compound-specific issues.
2. Species-specific plasma will be purchased from commercial sources and will be used as the blank (control) matrix for assay validation and stability assessments as well as calibration and quality control sample preparation. Estimated cost includes up to 300 mL of rat plasma.
3. The Sponsor will supply or reimburse for the test article(s) and suitable internal standard(s) (all with % purity ≥ 98%). Surcharges may apply for supplies that run outside the normal budget for this work.
4. Final price depends on the technical details in the final protocol and will be set forth in a Work Order. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.

Fee and Payment Schedule:
50% upon signature of the Proposal
40% upon completion of analysis
10% upon issuance of Draft Report

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

back to Proposal Summary

WIL Research Laboratories LLC General Terms and Conditions

1. SERVICES AND COMPLIANCE. WIL will use commercially reasonable efforts to perform specific authorized services or studies ("Services") as set forth in the Proposal. WIL will comply with all laws, rules and regulations (collectively, "Laws") applicable to the Services performed. If any Laws change while Services are being performed, and such Laws, in WIL's reasonable judgment, necessitate a change in the Proposal, (a) WIL will submit to Sponsor a revised Proposal for Sponsor's review and acceptance prior to making any changes to Services and (b) WIL will not be required to perform any Service to the extent such performance would, in WIL's reasonable judgment, be in violation of a Law. In the event of a conflict between any applicable Laws, the Parties will mutually agree in writing as to the applicable Laws to be followed in WIL's performance of the Services. Sponsor will comply fully with all Laws applicable to the subject matter of the Services. Notwithstanding anything to the contrary contained herein, WIL may use one or more of its affiliates to perform the Services.
2. MODIFICATIONS. Sponsor will provide to WIL in writing any requested change to Services, and no such request, change, extension, revision or other modification to the Services or any Proposal will be binding unless agreed to in writing by the Parties.
3. COMPENSATION. The amount of all fees and expenses associated with the delivery to Sponsor of the Services are set forth in the Proposal. Sponsor will bear all taxes, fees and expenses other than those set forth in the Proposal. Invoices will be rendered in United States Dollars and provide for payment net 30 days. All invoices will be sent to Sponsor's address indicated in the Proposal, unless otherwise agreed to in writing by the Parties. WIL may request to increase the fees or expenses set forth in the Proposal to reflect any actual increase to its expenses incurred in connection with providing the Services. No such increase will be binding until consented to in writing by Sponsor, which such consent will not be unreasonably withheld. If Sponsor fails to pay an invoice within 45 days of its issuance date, WIL may, in its sole discretion, charge the Sponsor a late fee equal to 1.5% per month on the unpaid balance of such invoice until paid in full (including any assessed late fees) or treat such non-payment as notice by Sponsor to terminate the Services.
4. TERMINATION. (a) A Proposal or specific Services may be terminated as follows: (i) Sponsor may, at any time upon written notice to WIL, terminate the Proposal or specific Services for convenience. Such written notice must state the extent and the effective date of termination. Upon receipt of such notice, WIL will use commercially reasonable efforts to minimize costs to Sponsor resulting from such termination. (ii) WIL may terminate a Proposal or specific Services upon notice to Sponsor of Sponsor's breach or failure to perform any obligations required by this Agreement, including Sponsor's failure to care payment default within 45 days of invoice issuance. (iii) Either Party may terminate any Proposal upon 90 days' prior written notice to the other Party. (iv) either Party may terminate a Proposal or specific Services upon 30 days written notice if any episode of force majeure described in Section 10 continues for 30 or more days after notification from the other Party of such episode. (b) If Services or Proposal are terminated for any reason pursuant to this Section 4, Sponsor will pay to WIL: (i) all amounts for authorized Services rendered through the effective date of termination; (ii) all wind-down costs incurred by WIL resulting from such termination; and (iii) all of WIL's costs and expenses incurred in preparation for providing the Services, including those incurred prior to commencement of authorized Services and whether invoiced or not. (c) Sponsor may, at any time upon written notice to WIL, delay authorized Services. Sponsor will pay WIL's costs and expenses incurred related to any such delay, and WIL will use commercially reasonable efforts to mitigate such costs and expenses until WIL receives written notice to resume performance of Services. (d) These General Terms and Conditions will apply to any Services performed pursuant to the Proposal, notwithstanding that the Proposal has been terminated, and will terminate upon completion of all outstanding Services, unless otherwise agreed to in writing by the Parties.
5. SURVIVAL. Notwithstanding the termination of the Proposal or specific Services thereunder, Sections 3 (Compensation), 4 (Termination), 5 (Survival), 6 (Intellectual Property & Work Product), 9 (Indemnification & Limiting Liability), 11 (Governing Law & Jurisdiction) and 13 (Miscellaneous) of these General Terms and Conditions will survive, unless otherwise agreed to in writing by the Parties.
6. INTELLECTUAL PROPERTY & WORK PRODUCT. Subject to the last sentence of this Section 6, all information or data collected, and all discoveries, inventions or improvements, whether patentable or not, other than WIL IP (as defined below), arising out of the performance of Services and relating to the articles or substances studied or the use thereof will be owned by Sponsor ("Sponsor IP"). At the request and sole expense of Sponsor, WIL will assign to Sponsor any and all of WIL's right, title and interest in Sponsor IP. Sponsor has no property rights in WIL's testing methods, practices, procedures, tests, test apparatus, equipment or information related to the conduct of WIL's business, or any inventions, improvements or developments related thereto ("WIL IP"). As between the Parties, WIL IP is the sole and exclusive property of WIL. Upon payment in full by Sponsor for all amounts invoiced hereunder, all tissues, tissue blocks, specimens, slides, material and data prepared or generated by WIL in the course of performing Services for Sponsor hereunder ("Work Product") will be owned by Sponsor and will be transferred to Sponsor upon its request after payment of such amounts.
7. INDEPENDENT CONTRACTOR. WIL is an independent contractor and that no provision in the Proposal, or any agreement subject to these General Terms and Conditions, will be construed to make WIL an employee, agent or representative of Sponsor, or be deemed to create a partnership or joint venture between the Parties. Neither Party will hold itself out to third persons as purporting to act on behalf of, or serving as the agent of, the other Party.
8. WARRANTY. Other than as specifically set forth in Section 1, WIL makes no representations or warranties concerning the Services.
9. INDEMNIFICATION & LIMITING LIABILITY. WIL will indemnify, defend and hold harmless Sponsor, its directors, officers, equityholders and employees ("Sponsor Indemnitees") from and against all third party loss or damage (including

reasonable attorney fees and expenses) arising from (a) WIL's material breach of this Agreement or (b) WIL's negligence or willful misconduct in the performance of the Services, except to the extent such loss or damage arises from the negligence or willful misconduct of a Sponsor Indemnitee or Sponsor's material breach of the Agreement. Sponsor will indemnify, defend and hold harmless WIL and its affiliates and their respective directors, officers, equityholders and employees ("WIL Indemnitees") from and against all third party loss or damage (including reasonable attorney fees and expenses) arising from (a) Sponsor's material breach of this Agreement, (b) Sponsor's negligence or willful misconduct or (c) Sponsor's use or exploitation of any Sponsor IP, Work Product or Sponsor Confidential Information, except to the extent such loss or damage arises from the negligence or willful misconduct of a WIL Indemnitee or WIL's material breach of this Agreement. Under no circumstances will either Party be liable to the other for any indirect, consequential, punitive, exemplary or special damages, including lost profits or cost of replacement materials. Subject to any limitations on remedies set forth herein, in no event will WIL be liable to Sponsor under this Agreement for any amounts in excess of the amount paid by Sponsor to WIL for Services provided hereunder. If WIL commits a deviation during the performance of Services that causes the results of such Services to be unusable for Sponsor's stated purposes as defined in the relevant Protocol, then at Sponsor's election, WIL will either (i) rerun that part of the Services affected by such deviation or (ii) refund to Sponsor the sums paid WIL as of that date with respect to such Services. The remedies provided in the immediately foregoing sentence are the Sponsor's (and the other Sponsor Indemnitees') sole and exclusive remedy with respect to WIL's deviations in the performance of Services. The remedies provided in this Section 9 are the sole and exclusive remedies available to the Sponsor Indemnitees with respect to any breach of any representation, warranty or agreement in the Proposal, or otherwise in respect of the Services contemplated by the Proposal (whether in contract, tort, strict liability or otherwise).

10. FORCE MAJEURE. Neither Party will be liable for any delay in performing its obligations (other than payment obligations) under the Proposal if its performance is delayed or prevented by acts of God, fire, terrorist acts, explosion, war, riots, strikes, law or any other cause (except financial) beyond such Party's reasonable control, but only to the extent of such disability. If performance required by the Proposal fails during or subsequent to the occurrence of a force majeure event, performance will be deferred for a period of time equal to the period of disability resulting from force majeure.

11. GOVERNING LAW; JURISDICTION. This Agreement will be construed in accordance with and governed by the laws of the State of Ohio (without regard to any choice or conflicts of law rules that would cause the application of the laws of any other jurisdiction). The Parties irrevocably submit to the personal jurisdiction of the state and federal courts of the State of Ohio, and agree that such courts are the appropriate, exclusive and convenient forum for, and will have exclusive jurisdiction over, any action or dispute arising out of this Agreement or relating to any of the Services, and the Parties irrevocably waive any right to claim that such forum is inconvenient. Neither Party will bring suit with respect to any action or dispute arising out of this Agreement or relating to any of the Services in any court or jurisdiction other than the above specified courts. The preceding sentence will not limit the rights of the Parties to obtain execution of a judgment in any other jurisdiction.

12. ASSIGNMENT. The Proposal subject to these General Terms and Conditions, and any performance thereunder, constitutes a personal services contract and may not be assigned by either Party without the express written consent of the other, which consent may not be unreasonably withheld, except that either Party may assign this contract without consent in connection with a transaction resulting in (a) a change of control with respect to such Party or (b) the acquisition of all or substantially all of such Party's assets by such assignee.

13. MISCELLANEOUS. [Insurance] WIL will maintain in full force and effect during the performance of Services, a policy or policies of insurance commensurate with industry standards for services substantially similar to the Services performed by WIL. [Delivery and Transfer] Any materials or Work Product shipped to WIL by Sponsor or a third party, or shipped by WIL to Sponsor or to a third Party, shall be at Sponsors expense. Therefore, Sponsor will pay any shipping or transportation costs and taxes, including any import or export duties, fees, and taxes. All Work Product will be appropriately packaged and labeled pursuant to WIL's standard operating procedures and delivered to a common carrier for shipment. Sponsor will hold WIL harmless from and against all loss or damage or claims of loss or damage to any Work Product during shipment by a common carrier. Sponsor will also pay the insurance premium and will notify WIL, in writing, of its desire to insure shipments at a rate that exceeds the common carrier's standard liability limit. In the event a claim results, Sponsor shall be responsible for substantiating (if required by the insurer) the value of the Work Product and for seeking reimbursement of any loss. [Severability] If a court of competent jurisdiction finds a provision of these General Terms and Conditions, the Proposal, or any agreement between the Parties subject hereto, to be invalid or contrary to public policy, the provisions not so found will remain in effect and binding upon the Parties. The Parties will agree in good faith to replace any invalid or unenforceable provision with a valid and enforceable provision that expresses as closely as possible the intention of the original provision. [Publications] Neither Party will use the name of the other Party or the other Party's employees in any advertising, sales promotional material, or in any publication without such other Party's prior written consent. [Dispute Resolution] The Parties will attempt in good faith to resolve any dispute arising hereunder prior to taking any legal action. If Parties are unable to resolve any such dispute within 30 days, each Party may seek any legal remedy available in accordance with these General Terms and Conditions. Notwithstanding the foregoing, either Party may seek interim legal relief in a court of competent jurisdiction if the other Party's breach of their obligations under any agreement subject hereto would reasonably be expected to cause such Party irreparable harm. [Precedence] No modification or waiver of the provisions of these General Terms and Conditions shall be valid or binding on either Party unless in writing and signed by both Parties. Unless otherwise expressly agreed to in writing by the Parties, in the event a Proposal, Protocol, or any other agreement between the Parties hereto conflict with or contradict these General Terms and Conditions, then these General Terms and Conditions shall control. [Counterparts] Any agreement between the Parties related to the Services (including any Proposal) may be executed in counterparts, each of which will be deemed an original, and all of which together will be deemed to be one and the same instrument. Signatures

to any agreement between the Parties related to the Services transmitted by facsimile transmission, by electronic mail in "portable document format" (".pdf") or similar form or by any other electronic means (*e.g.* DocuSign) intended to preserve the original graphic and pictorial appearance of a document will have the same effect as physical delivery of the paper document bearing the original signatures, and will be deemed original signatures by both Parties.

[*Remainder of left blank*]

WIL RESEARCH LABORATORIES LLC CANCELLATION AND DELAY POLICY

Timing	Cancellation Fee	Delay Fee
More than 45 days prior to animal arrival.	10% of the total fee under the signed proposal.	No fee.
Less than 45 days prior to animal arrival.	20% of the total fee under the signed proposal, plus Costs Incurred (as defined below).	$2,100 per day for each room utilized
Any time after animal receipt.	50% of the total fee under the signed proposal, plus the cost of any animals ordered under the proposal and any Costs Incurred.	$2,100 per day for each room utilized plus any Costs Incurred.
Non-animal related studies.	Costs Incurred. for study preparation and conduct including but not limited to time and materials related to protocol preparation and protocol activities, instrument set up, study termination, and reporting (if required)	No fee.

- Unless otherwise expressly agreed to in writing by the Parties, the fees and obligations detailed in this policy are in addition to the written terms and conditions, or any other agreement, as may be agreed to by the Parties.
- Actual fees may vary depending on the nature and specifications of the services (*e.g.* Costs Incurred, species, the number of animals involved, unique animal specifications).
- WIL Research Laboratories LLC ("WIL") shall, in good faith, use commercially reasonable efforts to mitigate costs incurred resulting from any cancellation or delay.
- Upon Sponsor's request, WIL shall make a good faith effort to reschedule cancelled or delayed services as close as possible to the requested time frame.
- Cost Incurred may (i) prior to commencement of services include any reasonable costs and expenses related to study preparation, time and materials related to protocol development, (ii) following cancelation or delay include any reasonable costs and expenses related to maintenance of animals or materials, reoccurring costs related to such delay, any reporting (if required), and any wind-down costs resulting from such cancellation or delay (*e.g.* necropsy). Additionally, in each case, if large animals were ordered or used, then Costs Incurred shall also include the cost to maintain such large animals which such cost will not be less than $2,100 per day for each room utilized, for a minimum of 30 days.
- This information is provided at the request of Sponsor and is intended for the sole use of Sponsor in regards to the services provided by WIL. Further, this information is considered confidential and is not to be copied or shared with any third party unless approved in writing by WIL prior to any disclosure.

APPENDIX 1 (CORRECTED)

HSIA halogenated solvents industry alliance, inc.

MEMORANDUM

To: Docket EPA-HQ-OPPT-2016-0163

From: Faye Graul
Executive Director

Date: March 16, 2017

Subj: Trichloroethylene Drinking Water Study

Attached please find a copy of Protocol Number WIL-459501 titled An Oral (Drinking Water) Study of the Effects of Trichloroethylene (TCE) on Fetal Heart Development in Sprague Dawley Rats. The Protocol was signed on October 6, 2016 and the in-life portion of the study was conducted during October and November, 2016. Unfortunately, the concentrations of TCE measured in the drinking water solutions were found to be below the acceptable target range of 100% ± 10%, invalidating the study. The laboratory is conducting additional studies to identify the source of the deviations and the study will be rerun as soon as the dosing methodological issues are resolved and scheduling permits.

3033 Wilson Boulevard, Suite 700 • Arlington, VA 22201
www.hsia.org

WIL RESEARCH

5 August 2016
Proposal: 15.04279

Proposal for Halogenated Solvents Industry Alliance

Proposal provided by:
WIL Research
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Ashland, OH 44805
USA
Tel: 419-289-8700
Fax: 419-289-3650
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Contact information:
Brad Haynes, MBA
Business Development Director
Tel: 440-596-9993
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Eddie Sloter, PhD
Scientific Director
Tel: 419-282-6941
E-mail: eddie.sloter@wilresearch.com

Proposal Summary

Study	Base Study Fee	Optional			Total Study Fee	
		AC	BioAC	TK Report		Authorized
A (5-Group) Prenatal Developmental Toxicity Study of TCE Administered by Drinking Water in Sprague Dawley Rats	$168,000	$12,400	$15,730	$4,100	$200,230	X
Analytical Validation, Homogeneity, and Stability Study of the Analyte in Aqueous Formulations	$24,160	-	-	-	$24,160	X
Development and Testing of an LC-MS/MS Method for the Quantification of Test Article (TCE) and a Major Metabolite (TCA) in Rat Plasma	$11,050	-	-	-	$11,050	X
Validation of an LC-MS/MS Method for the Quantification of Test Article in Rat Plasma	$28,750	-	-	-	$28,750	X

***Fee and Payment Schedules are subject to credit approval.**

Authorization Statement

Halogenated Solvents Industry Alliance ("Sponsor") hereby awards the above described proposal (the "Proposal") to WIL Research Laboratories, LLC ("WIL") (each a "Party"), and requests WIL to proceed with the necessary activities to initiate these Services, including but not limited to, Protocol development, Study room reservation, and definitive scheduling of Services.

This Proposal, the performance of Services, and each Party's obligations herein are governed by and subject to the WIL Research Laboratories LLC General Terms and Conditions attached hereto (the "General Terms and Conditions"). The General Terms and Conditions are hereby incorporated by reference to this Proposal in their entirety. By executing below, Sponsor acknowledges and represents, and the undersigned person executing this Proposal on behalf of Sponsor certifies, that such person has read and Sponsor agrees to the provisions set forth in the General Terms and Conditions.

This Proposal (including the relevant Protocol), together with the General Terms and Conditions and the Confidentiality Agreement between the Parties dated [08/08/14], constitutes the entire agreement (the "Agreement") between the Parties with respect to the subject matter contained herein. There are no oral or written promises, terms, conditions, or obligations other than those contained in this Agreement. This Agreement supersedes all prior negotiations, representations or other agreements, either written or oral, between the Parties on the subject matter related herein. No modification or waiver of the provisions of this Proposal, the General Terms and Conditions or the Confidentiality Agreement shall be valid or binding on either Party unless agreed to in writing by each Party.

In the event the terms of this Proposal or any other agreement between the parties hereto contradict any provision of the General Terms and Conditions, the General Terms and Conditions shall control unless expressly agreed to in writing by each Party herein.

Any notices given hereunder shall be sent by fax or email, with a confirmation copy sent via overnight courier to the following addresses (or such other address as a party may designate as a notice address in a written notice to the other party) and shall be deemed received when delivered (or if received on a weekend or holiday, on the next business day thereafter) as follows:

If to Sponsor: Name: John Bell
Title: Director, Scientific Programs
Company: Halogenated Solvents Industry Alliance, Inc.
Address: 3033 Wilson Boulevard
Suite 700
Arlington, VA 22201
Phone: 202 286 6464
Email: jbell@hsia.org

If to WIL: John Maxwell
Vice President
WIL Research Laboratories, LLC
1407 George Road
Ashland, OH 44805
Phone: (419) 289-8700
Email: john.maxwell@wilresearch.com

With a copy to: Corporate Counsel
WIL Research Laboratories, LLC
8025 Lamon Avenue
Skokie, IL 60077
Email: jon.galli@wilresearch.com

By executing this document Sponsor understands, acknowledges and agrees to the financial responsibility for all costs and expenses in accordance with this Proposal including those incurred by WIL in preparation of the Study. Any modification that requires an increase in cost subsequent from the effective date of this Proposal will be adjusted through a Study Modification.

Signature of Authorized Sponsor Representative — Date: August 8, 2016

Name: John Bell, Ph.D., DABT

Title: Director, Scientific Programs

Company: Halogenated Solvents Industry Alliance, Inc.

Company Address: Suite 700

3033 Wilson Boulevard

Arlington, VA 22201

Email Address (invoices will only be sent as a PDF to this email address):

jbell@hsia.org

A (5-Group) Prenatal Developmental Toxicity Study of TCE Administered by Drinking Water in Sprague Dawley Rats
Compliance: GLP, OECD
Guidelines: Modified OECD 414

Group	Toxicology Animals (145)	
	Toxicology Females (150)	Maternal TK (20)
1	25	4
2	25	4
3	25	4
4	25	4
5	25	4
6	25	-

Objective:	To detect potential adverse effects on the pregnant female and on the development of the embryo and fetus consequent to exposure of the female starting the day after mating (Gestation Day 1) through implantation and gestation until one day prior to expected parturition.
Animals[3]:	Female Sprague Dawley Rats Crl:CD(SD) 170 animals on study, 212 animals ordered Untreated sexually mature males of the same strain and source will be used to induce pregnancies.
Groups:	1 control group, 4 test article-treated groups and 1 positive control group.
Dose Levels[3]:	Highest dose will be 1100 ppm in drinking water based on a previous study conducted by Johnson et al.
Test Substance Preparation:	Prepared at a frequency consistent with established stability.
Sampling of Formulations:	From the first and last preparations. Samples analyzed at WIL Research (optional).
Test Substance Administration:	Via drinking water (glass water bottles) from gestation day 1 until the day of scheduled necropsy at the end of gestation, inclusively. Day evidence of mating is confirmed is gestation day 0. Group 6 (positive control group) dosed via oral gavage from Gestation Day 6-15, inclusively.
Viability Observations:	Twice daily observations for moribundity and mortality.
Clinical Observations:	Once daily.
Body Weights:	Toxicology Animals: Gestation days 0-20 (daily). Toxicokinetic Animals: Gestation days 0-20 (daily).
Food Consumption:	Toxicology Animals: Gestation days 0-20 (daily). Toxicokinetic Animals: Not recorded.
Toxicokinetics:	Maternal TK Phase – Blood samples collected from each dam on GD 8, GD 16 and again at the end of the administration period (GD 20) from 4 maternal toxicokinetic animals/group/time point at a single time point (60 maternal samples). Samples can be analyzed at WIL Research (optional). Fetal TK – Immediately following the final maternal tk blood collection on GD 20, each dam will be euthanized and fetal blood will be collected from the umbilical vessel of each fetus and pooled by litter (20 pooled fetal samples). Samples can be analyzed at WIL Research (optional).
Scheduled Laparohysterectomy:	Toxicokinetic Animals: Gestation day 20; Determination of pregnancy status only and fetal blood collected as required. Toxicology Animals: Gestation day 20; Examination of uterine contents: determination of pregnancy status, gravid uterine weights, gross evaluation

of placenta and count of corpora lutea, implantation sites, early and late resorptions and viable and nonviable fetuses.

Fetal Observations: External and fresh visceral examinations of all viable fetuses for developmental variations and malformations, sex ratios and body weights. The carcass of each fetus will be preserved and retained for possible future skeletal evaluation.

Quality Assurance: The study will be conducted in compliance with Good Laboratory Practice (GLP) standards and will be monitored by the Quality Assurance Unit.

Reports: Audited Draft Report and Final Report.

Archiving: For a period of six months after study completion.

5-Group Base Study Fee (Full Fetal Visceral Evaluations) [1] $166,000

Optional Support Fees:

Analytical Chemistry (AC): [2] $3,400/set

Concentration determination (1st preparation with concurrent homogeneity):	$3,400
Resuspension homogeneity (1 interval):	$3,400
Concentration determination (last preparation):	$3,400
Sample analysis report:	$2,200
Total Study-specific AC:	$12,400

Bioanalytical Chemistry (BioAC): [4]

Sample analysis - 80 samples @ $85/sample (minimum batch 100 samples):	$8,500
Dilution repeats - 30 samples @ $85/sample[5] (estimated 10% of samples; minimum batch 30 samples):	$2,550
Incurred sample reanalysis - 8 samples @ $85/sample:	$680
Report Fee[6]:	$4,000
Total Study-specific BioAC:	$15,730

Toxicokinetic Report:

Preparation of a toxicokinetic report from the maternal and fetal exposure data for a single analyte and single dose route. Preliminary toxicokinetic results will be available upon request and will typically be provided within two business days of availability of bioanalytical data.

TK Report: $4,100

1. Final price depends on the technical details in the final protocol and will be set forth in a Work Order. Base study fee is exclusive of analytical and bioanalytical chemistry support and toxicokinetic evaluation. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.
2. A minimum of 20 litters per group is recommended in this guideline.
3. Studies that do not establish a maternal NOAEL may be acceptable under this guideline.
4. These fees are considered estimates until the method has been developed. The fee for method development and validation is not included. Upon completion of the method development, the sponsor will be notified if different analysis fees apply. The costs also assume typical sample processing as well as standard analytical detection will be sufficient. Long processing procedures, long analytical run times, and mass spectrometric detection will result in an increased fee.
5. These fees are considered estimates. Additional samples and dilution repeats beyond 10% will be charged at a rate of $85/sample. The Sponsor will be notified in writing, prior to application of any such fees.
6. A report fee will be waived if there are ≥ 150 samples analyzed.

Fee and Payment Schedule:
20% upon signature of the Proposal
40% 45 days prior to animal arrival
30% upon completion of in-life
10% upon issuance of Draft Report

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

back to Proposal Summary

Analytical Validation, Homogeneity, and Stability Study of the Analyte in Aqueous Formulations
Compliance: GLP

Development and validation of a method for the determination of analyte concentration in aqueous formulations:

Method development usually includes (but is not limited to) the following activities: (1) investigation of potential solubility limitations; (2) the analysis of standards prepared in an appropriate solvent to establish chromatography, including retention times, resolution, and to check proportionality of response; (3) the analysis of the analyte prepared in the matrix to confirm the presence or absence of interferences, to evaluate potential stability limitations, and to evaluate response proportionality. Method development will be billed at a rate of $260/hour and will not exceed the amount proposed without sponsor approval.

Validation will be conducted using the current WIL SOP guidelines for the assessment of system suitability, method specificity/selectivity, intra- and inter-session method calibration acceptability, intra- and inter-session method accuracy and precision, ruggedness, and processed sample stability. A minimum of three validation sessions will be conducted. All laboratory work associated with validations will be conducted in accordance with applicable GLP regulations.

Homogeneity and stability assessment of analyte in aqueous formulations:

Testing includes the assessment of test article homogeneity in formulations spanning the range of concentration anticipated on future studies. In addition, resuspension homogeneity and stability will be assessed following a single storage duration. Additional stability time-points can be added for an additional fee. All laboratory work associated with sample analysis will be conducted in accordance with applicable GLP regulations.

Quality Assurance: The study will be conducted in compliance with Good Laboratory Practice (GLP) standards and will be monitored by the Quality Assurance Unit.

Reports: Audited Draft Report and Final Report.

Archiving: For a period of six months after study completion.

Summary of Fees:

Method Development (up to 16 hours):	$4,160
Method Validation in Aqueous Formulations: [2]	$11,000
Homogeneity and Stability Assessments in Aqueous Formulations: [2]	$6,800
Analytical Report:	$2,200
Base Fee [1]	$24,160

1. Final price depends on the technical details in the final protocol and will be set forth in a Work Order. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.
2. These fees are considered estimates until the method has been developed. Upon completion of the method development, the sponsor will be notified if different analysis fees apply. The costs also assume that typical sample processing as well as standard analytical detection will be sufficient. Long processing procedures, long analytical run times, and mass spectrometric detection will result in an increased fee.

Fee and Payment Schedule:
50% upon signature of the Proposal
40% upon completion of analysis
10% upon issuance of Draft Report

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

back to Proposal Summary

Development and Testing of an LC-MS/MS Method for the Quantification of Test Article (TCE) and a Major Metabolite (TCA) in Rat Plasma
Compliance: Non-GLP

Development:	A fit-for-purpose LC-MS/MS method will be developed for the quantification of test article and one major metabolite in rat plasma. Appropriate chromatographic, mass spectrometric, and sample extraction procedures will be developed to achieve the sensitivity and specifications needed to support non-clinical studies of the test article.
Testing:	Once a suitable method has been developed, testing will be conducted that will include quantifying standards, quality control samples, and blanks to estimate the sensitivity, linearity, accuracy, and reproducibility of the procedure, and to ensure that the proper concentration range and conditions are selected prior to validation or analysis of study samples (as applicable). WIL Research will provide the Sponsor with timely updates on progress.
Quality Assurance:	The study will not be monitored or audited by the Quality Assurance Unit.
Archiving:	For a period of six months after study completion.

Summary of Fees:

Development and Testing [1,2,3];	
24 hours @ $270/hour:	$6,480
Pre-Validation Testing 16 hours @ $270/hour:	$4,320
Materials:	$250
Base Study Fee [4]	$11,050

1. Method development and pre-validation will be billed at a rate of $270/hr. These activities will not be audited.
2. Species-specific plasma will be purchased from commercial sources and will be used as the blank (control) matrix. Estimated cost includes up to 100 mL of rat plasma.
3. The Sponsor will supply or reimburse for the test article(s) and suitable internal standard(s) (all with % purity ≥ 98%). Surcharges may apply for supplies that run outside the normal budget for this work.
4. Final price depends on the technical challenges encountered; additional time beyond that estimated above may be required; the Sponsor will be contacted for approval of any additional work. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.

Fee and Payment Schedule:
50% upon signature of the Proposal
50% upon completion of analysis

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

Back to Proposal Summary

Validation of an LC-MS/MS Method for the Quantification of Test Article in Rat Plasma
Compliance: GLP

Validation:	Validation will be performed according to the FDA "Guidelines for Bioanalytical Method Validation" and 21 CFR Part 58, Good Laboratory Practice for Non-Clinical Laboratory Studies (revised as of April 1, 2007). Testing will include a minimum of 3 runs of matrix standard curves, along with at least 4 QC concentrations (LLOQ, low, medium, high) and at least 18 replicates total at each concentration. Intra-assay and inter-assay precision and accuracy of the QC samples will be determined. Validation will also include evaluation of linearity and limit of quantification, reproducibility, dilution effect, recovery, selectivity, carryover and processing, freeze-thaw, whole blood, and stock solution stability.
Stability:	All plasma stability evaluations will be performed at the low, high, and dilution QC levels. Long-term frozen storage stability testing at one time point and at one temperature is included in the validation fee.
Additional Fees:	Additional fees, $4,500/occasion, may be applied if additional stability time points/temperatures are requested by the Sponsor.
Protocol:	A protocol will be prepared by WIL Research for the validation. The Sponsor and/or Sponsor's representative will review the draft protocol and approve the final protocol.
Quality Assurance:	The study will be conducted in compliance with Good Laboratory Practice (GLP) standards and will be monitored by the Quality Assurance Unit.
Reports:	An audited draft validation report will be prepared by WIL Research and the Sponsor will be given time to review and comment on the report before it is finalized. The final bioanalytical procedure will be provided with the validation report. Requests for specific formatting for protocols and/or reports or multiple revisions may incur additional fees.
Archiving:	For a period of six months after study completion.

Summary of Fees:

Validation for Quantification [1,2,3]

Validation:	$28,000
Additional stability time points @ $4,500/time point:	TBD
Materials:	$750
Base Study Fee [4]	$28,750

1. The validation fee assumes quantification of a single analyte and is considered an estimate until the method has been developed. Upon completion of the method development, the sponsor will be notified if the base study fee will change. The final validation fee is dependent upon, but not limited to the suitability of the IS compound, LC run time, complexity and number of extractions, and other compound-specific issues.
2. Species-specific plasma will be purchased from commercial sources and will be used as the blank (control) matrix for assay validation and stability assessments as well as calibration and quality control sample preparation. Estimated cost includes up to 300 mL of rat plasma.
3. The Sponsor will supply or reimburse for the test article(s) and suitable internal standard(s) (all with % purity ≥ 98%). Surcharges may apply for supplies that run outside the normal budget for this work.
4. Final price depends on the technical details in the final protocol and will be set forth in a Work Order. This quotation is valid for 90 days with respect to authorization of the study, provided the study is initiated within six months from the date of this outline; thereafter the study fee is subject to review.

Fee and Payment Schedule:
50% upon signature of the Proposal
40% upon completion of analysis
10% upon issuance of Draft Report

Sponsor Number:_____

Study Monitor/ Company Contact: _____ Purchase Order No. (if applicable):_____

back to Proposal Summary

WIL Research Laboratories LLC General Terms and Conditions

1. SERVICES AND COMPLIANCE. WIL will use commercially reasonable efforts to perform specific authorized services or studies ("Services") as set forth in the Proposal. WIL will comply with all laws, rules and regulations (collectively, "Laws") applicable to the Services performed. If any Laws change while Services are being performed, and such Laws, in WIL's reasonable judgment, necessitate a change in the Proposal, (a) WIL will submit to Sponsor a revised Proposal for Sponsor's review and acceptance prior to making any changes to Services and (b) WIL will not be required to perform any Service to the extent such performance would, in WIL's reasonable judgment, be in violation of a Law. In the event of a conflict between any applicable Laws, the Parties will mutually agree in writing as to the applicable Laws to be followed in WIL's performance of the Services. Sponsor will comply fully with all Laws applicable to the subject matter of the Services. Notwithstanding anything to the contrary contained herein, WIL may use one or more of its affiliates to perform the Services.
2. MODIFICATIONS. Sponsor will provide to WIL in writing any requested change to Services, and no such request, change, extension, revision or other modification to the Services or any Proposal will be binding unless agreed to in writing by the Parties.
3. COMPENSATION. The amount of all fees and expenses associated with the delivery to Sponsor of the Services are set forth in the Proposal. Sponsor will bear all taxes, fees and expenses other than those set forth in the Proposal. Invoices will be rendered in United States Dollars and provide for payment net 30 days. All invoices will be sent to Sponsor's address indicated in the Proposal, unless otherwise agreed to in writing by the Parties. WIL may request to increase the fees or expenses set forth in the Proposal to reflect any actual increase to its expenses incurred in connection with providing the Services. No such increase will be binding until consented to in writing by Sponsor, which such consent will not be unreasonably withheld. If Sponsor fails to pay an invoice within 45 days of its issuance date, WIL may, in its sole discretion, charge the Sponsor a late fee equal to 1.5% per month on the unpaid balance of such invoice until paid in full (including any assessed late fees) or treat such non-payment as notice by Sponsor to terminate the Services.
4. TERMINATION. (a) A Proposal or specific Services may be terminated as follows: (i) Sponsor may, at any time upon written notice to WIL, terminate the Proposal or specific Services for convenience. Such written notice must state the extent and the effective date of termination. Upon receipt of such notice, WIL will use commercially reasonable efforts to minimize costs to Sponsor resulting from such termination. (ii) WIL may terminate a Proposal or specific Services upon notice to Sponsor of Sponsor's breach or failure to perform any obligations required by this Agreement, including Sponsor's failure to care payment default within 45 days of invoice issuance. (iii) Either Party may terminate any Proposal upon 90 days' prior written notice to the other Party. (iv) either Party may terminate a Proposal or specific Services upon 30 days written notice if any episode of force majeure described in Section 10 continues for 30 or more days after notification from the other Party of such episode. (b) If Services or Proposal are terminated for any reason pursuant to this Section 4, Sponsor will pay to WIL: (i) all amounts for authorized Services rendered through the effective date of termination; (ii) all wind-down costs incurred by WIL resulting from such termination; and (iii) all of WIL's costs and expenses incurred in preparation for providing the Services, including those incurred prior to commencement of authorized Services and whether invoiced or not. (c) Sponsor may, at any time upon written notice to WIL, delay authorized Services. Sponsor will pay WIL's costs and expenses incurred related to any such delay, and WIL will use commercially reasonable efforts to mitigate such costs and expenses until WIL receives written notice to resume performance of Services. (d) These General Terms and Conditions will apply to any Services performed pursuant to the Proposal, notwithstanding that the Proposal has been terminated, and will terminate upon completion of all outstanding Services, unless otherwise agreed to in writing by the Parties.
5. SURVIVAL. Notwithstanding the termination of the Proposal or specific Services thereunder, Sections 3 (Compensation), 4 (Termination), 5 (Survival), 6 (Intellectual Property & Work Product), 9 (Indemnification & Limiting Liability), 11 (Governing Law & Jurisdiction) and 13 (Miscellaneous) of these General Terms and Conditions will survive, unless otherwise agreed to in writing by the Parties.
6. INTELLECTUAL PROPERTY & WORK PRODUCT. Subject to the last sentence of this Section 6, all information or data collected, and all discoveries, inventions or improvements, whether patentable or not, other than WIL IP (as defined below), arising out of the performance of Services and relating to the articles or substances studied or the use thereof will be owned by Sponsor ("Sponsor IP"). At the request and sole expense of Sponsor, WIL will assign to Sponsor any and all of WIL's right, title and interest in Sponsor IP. Sponsor has no property rights in WIL's testing methods, practices, procedures, tests, test apparatus, equipment or information related to the conduct of WIL's business, or any inventions, improvements or developments related thereto ("WIL IP"). As between the Parties, WIL IP is the sole and exclusive property of WIL. Upon payment in full by Sponsor for all amounts invoiced hereunder, all tissues, tissue blocks, specimens, slides, material and data prepared or generated by WIL in the course of performing Services for Sponsor hereunder ("Work Product") will be owned by Sponsor and will be transferred to Sponsor upon its request after payment of such amounts.
7. INDEPENDENT CONTRACTOR. WIL is an independent contractor and that no provision in the Proposal, or any agreement subject to these General Terms and Conditions, will be construed to make WIL an employee, agent or representative of Sponsor, or be deemed to create a partnership or joint venture between the Parties. Neither Party will hold itself out to third persons as purporting to act on behalf of, or serving as the agent of, the other Party.
8. WARRANTY. Other than as specifically set forth in Section 1, WIL makes no representations or warranties concerning the Services.
9. INDEMNIFICATION & LIMITING LIABILITY. WIL will indemnify, defend and hold harmless Sponsor, its directors, officers, equityholders and employees ("Sponsor Indemnitees") from and against all third party loss or damage (including

reasonable attorney fees and expenses) arising from (a) WIL's material breach of this Agreement or (b) WIL's negligence or willful misconduct in the performance of the Services, except to the extent such loss or damage arises from the negligence or willful misconduct of a Sponsor Indemnitee or Sponsor's material breach of the Agreement. Sponsor will indemnify, defend and hold harmless WIL and its affiliates and their respective directors, officers, equityholders and employees ("WIL Indemnitees") from and against all third party loss or damage (including reasonable attorney fees and expenses) arising from (a) Sponsor's material breach of this Agreement, (b) Sponsor's negligence or willful misconduct or (c) Sponsor's use or exploitation of any Sponsor IP, Work Product or Sponsor Confidential Information, except to the extent such loss or damage arises from the negligence or willful misconduct of a WIL Indemnitee or WIL's material breach of this Agreement. Under no circumstances will either Party be liable to the other for any indirect, consequential, punitive, exemplary or special damages, including lost profits or cost of replacement materials. Subject to any limitations on remedies set forth herein, in no event will WIL be liable to Sponsor under this Agreement for any amounts in excess of the amount paid by Sponsor to WIL for Services provided hereunder. If WIL commits a deviation during the performance of Services that causes the results of such Services to be unusable for Sponsor's stated purposes as defined in the relevant Protocol, then at Sponsor's election, WIL will either (i) rerun that part of the Services affected by such deviation or (ii) refund to Sponsor the sums paid WIL as of that date with respect to such Services. The remedies provided in the immediately foregoing sentence are the Sponsor's (and the other Sponsor Indemnitees') sole and exclusive remedy with respect to WIL's deviations in the performance of Services. The remedies provided in this Section 9 are the sole and exclusive remedies available to the Sponsor Indemnitees with respect to any breach of any representation, warranty or agreement in the Proposal, or otherwise in respect of the Services contemplated by the Proposal (whether in contract, tort, strict liability or otherwise).

10. FORCE MAJEURE. Neither Party will be liable for any delay in performing its obligations (other than payment obligations) under the Proposal if its performance is delayed or prevented by acts of God, fire, terrorist acts, explosion, war, riots, strikes, law or any other cause (except financial) beyond such Party's reasonable control, but only to the extent of such disability. If performance required by the Proposal fails during or subsequent to the occurrence of a force majeure event, performance will be deferred for a period of time equal to the period of disability resulting from force majeure.

11. GOVERNING LAW; JURISDICTION. This Agreement will be construed in accordance with and governed by the laws of the State of Ohio (without regard to any choice or conflicts of law rules that would cause the application of the laws of any other jurisdiction). The Parties irrevocably submit to the personal jurisdiction of the state and federal courts of the State of Ohio, and agree that such courts are the appropriate, exclusive and convenient forum for, and will have exclusive jurisdiction over, any action or dispute arising out of this Agreement or relating to any of the Services, and the Parties irrevocably waive any right to claim that such forum is inconvenient. Neither Party will bring suit with respect to any action or dispute arising out of this Agreement or relating to any of the Services in any court or jurisdiction other than the above specified courts. The preceding sentence will not limit the rights of the Parties to obtain execution of a judgment in any other jurisdiction.

12. ASSIGNMENT. The Proposal subject to these General Terms and Conditions, and any performance thereunder, constitutes a personal services contract and may not be assigned by either Party without the express written consent of the other, which consent may not be unreasonably withheld, except that either Party may assign this contract without consent in connection with a transaction resulting in (a) a change of control with respect to such Party or (b) the acquisition of all or substantially all of such Party's assets by such assignee.

13. MISCELLANEOUS. [Insurance] WIL will maintain in full force and effect during the performance of Services, a policy or policies of insurance commensurate with industry standards for services substantially similar to the Services performed by WIL. [Delivery and Transfer] Any materials or Work Product shipped to WIL by Sponsor or a third party, or shipped by WIL to Sponsor or to a third Party, shall be at Sponsors expense. Therefore, Sponsor will pay any shipping or transportation costs and taxes, including any import or export duties, fees, and taxes. All Work Product will be appropriately packaged and labeled pursuant to WIL's standard operating procedures and delivered to a common carrier for shipment. Sponsor will hold WIL harmless from and against all loss or damage or claims of loss or damage to any Work Product during shipment by a common carrier. Sponsor will also pay the insurance premium and will notify WIL, in writing, of its desire to insure shipments at a rate that exceeds the common carrier's standard liability limit. In the event a claim results, Sponsor shall be responsible for substantiating (if required by the insurer) the value of the Work Product and for seeking reimbursement of any loss. [Severability] If a court of competent jurisdiction finds a provision of these General Terms and Conditions, the Proposal, or any agreement between the Parties subject hereto, to be invalid or contrary to public policy, the provisions not so found will remain in effect and binding upon the Parties. The Parties will agree in good faith to replace any invalid or unenforceable provision with a valid and enforceable provision that expresses as closely as possible the intention of the original provision. [Publications] Neither Party will use the name of the other Party or the other Party's employees in any advertising, sales promotional material, or in any publication without such other Party's prior written consent. [Dispute Resolution] The Parties will attempt in good faith to resolve any dispute arising hereunder prior to taking any legal action. If Parties are unable to resolve any such dispute within 30 days, each Party may seek any legal remedy available in accordance with these General Terms and Conditions. Notwithstanding the foregoing, either Party may seek interim legal relief in a court of competent jurisdiction if the other Party's breach of their obligations under any agreement subject hereto would reasonably be expected to cause such Party irreparable harm. [Precedence] No modification or waiver of the provisions of these General Terms and Conditions shall be valid or binding on either Party unless in writing and signed by both Parties. Unless otherwise expressly agreed to in writing by the Parties, in the event a Proposal, Protocol, or any other agreement between the Parties hereto conflict with or contradict these General Terms and Conditions, then these General Terms and Conditions shall control. [Counterparts] Any agreement between the Parties related to the Services (including any Proposal) may be executed in counterparts, each of which will be deemed an original, and all of which together will be deemed to be one and the same instrument. Signatures

to any agreement between the Parties related to the Services transmitted by facsimile transmission, by electronic mail in "portable document format" (".pdf") or similar form or by any other electronic means (*e.g.* DocuSign) intended to preserve the original graphic and pictorial appearance of a document will have the same effect as physical delivery of the paper document bearing the original signatures, and will be deemed original signatures by both Parties.

[*Remainder of left blank*]

WIL RESEARCH LABORATORIES LLC CANCELLATION AND DELAY POLICY

Timing	Cancellation Fee	Delay Fee
More than 45 days prior to animal arrival.	10% of the total fee under the signed proposal.	No fee.
Less than 45 days prior to animal arrival.	20% of the total fee under the signed proposal, plus Costs Incurred (as defined below).	$2,100 per day for each room utilized
Any time after animal receipt.	50% of the total fee under the signed proposal, plus the cost of any animals ordered under the proposal and any Costs Incurred.	$2,100 per day for each room utilized plus any Costs Incurred.
Non-animal related studies.	Costs Incurred. for study preparation and conduct including but not limited to time and materials related to protocol preparation and protocol activities, instrument set up, study termination, and reporting (if required)	No fee.

- Unless otherwise expressly agreed to in writing by the Parties, the fees and obligations detailed in this policy are in addition to the written terms and conditions, or any other agreement, as may be agreed to by the Parties.
- Actual fees may vary depending on the nature and specifications of the services (*e.g.* Costs Incurred, species, the number of animals involved, unique animal specifications).
- WIL Research Laboratories LLC ("WIL") shall, in good faith, use commercially reasonable efforts to mitigate costs incurred resulting from any cancellation or delay.
- Upon Sponsor's request, WIL shall make a good faith effort to reschedule cancelled or delayed services as close as possible to the requested time frame.
- Cost Incurred may (i) prior to commencement of services include any reasonable costs and expenses related to study preparation, time and materials related to protocol development, (ii) following cancelation or delay include any reasonable costs and expenses related to maintenance of animals or materials, reoccurring costs related to such delay, any reporting (if required), and any wind-down costs resulting from such cancellation or delay (*e.g.* necropsy). Additionally, in each case, if large animals were ordered or used, then Costs Incurred shall also include the cost to maintain such large animals which such cost will not be less than $2,100 per day for each room utilized, for a minimum of 30 days.
- This information is provided at the request of Sponsor and is intended for the sole use of Sponsor in regards to the services provided by WIL. Further, this information is considered confidential and is not to be copied or shared with any third party unless approved in writing by WIL prior to any disclosure.